Transfusion Medicine Reviews 29 (2015) 259–267

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Adoptive Immunotherapies After Allogeneic Hematopoietic Stem Cell Transplantation in Patients With Hematologic Malignancies

Yu Xiong [a,c], Danièle Bensoussan [a,b], Véronique Decot [a,b,*]

[a] Unité de Thérapie Cellulaire et Tissus, CHU Nancy, Nancy, France
[b] Nancy Université, UL-UMR CNRS 7365, Faculté de Médecine, Vandoeuvre-lés-Nancy, Nancy, France
[c] Institute of Hepatobiliary Diseases of Wuhan University, Transplant Center of Wuhan University, Hubei Key Laboratory of Medical Technology on Transplantation, Zhongnan Hospital of Wuhan University, Wuhan, China

ARTICLE INFO

Available online 10 July 2015

Keywords:
Allogeneic hematopoietic stem cell transplantation
relapse
graft-versus-host disease
adoptive immunotherapies

ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is the only curative therapy for patients with chemotherapy-resistant hematologic malignancies that are usually fatal in absence of treatment. Hematopoietic stem cell transplantation is associated with significant early and late morbidity and mortality. Graft-versus-host disease, infections, and relapse are the most important causes of mortality after HSCT. Until now, these complications have been managed mainly with pharmacological drugs, but in some situations, this approach clearly shows its limit. As such, there is a significant need for novel therapies for the treatment of complications after allogeneic HSCT. In this review, the currently available adoptive immunotherapies offering an alternative in case of treatment failure of HSCT complications will be described. The results of the main clinical trials based on immune cell infusion will be discussed and the strategies aiming at maximizing cytotoxic T-lymphocyte, regulatory T-cell, natural killer cell, cytokine-induced killer cell, and γδ T-cell efficacies in the context of immunotherapy approaches after allogeneic HSCT in patients with hematologic malignancies will be gathered.

Contents

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative strategy for hematologic malignancies [1], solid malignancies [2], and other nonmalignant diseases [3]. Early and late complications after allo-HSCT include graft-versus-host disease (GVHD), disease relapse, and infections [4]. These complications limit the efficacy of hematopoietic stem cell transplantation (HSCT), and its outcome depends on numerous variables, such as the type of disease, age of the patient, stage of disease progression, and therapies used.

* Corresponding author at: Véronique Decot, PhD, Cell Therapy and Tissue Unit, CHU Nancy, Allée du Morvan, Vandoeuvre les Nancy, France, 54511.
E-mail address: v.decot@chu-nancy.fr (V. Decot).

http://dx.doi.org/10.1016/j.tmrv.2015.07.001
0887-7963/

Importantly, graft-versus-tumor (GVT) effects or recognition of cancer cells by donor T cells is the primary objective sought with this therapy. Unfortunately, GVHD and GVT are tightly associated, and the pathways of one can lead to the other. Therefore, novel methods of augmenting the GVT and treatments of complications after allo-HSCT are needed. This review will focus especially on current adoptive immunotherapeutic approaches (eg, cytotoxic T lymphocytes [CTLs], γδ T cells, cytokine-induced killer [CIK] cells, natural killer [NK] cells, and regulatory T cells [Tregs]) developed to treat the complications occurring after allo-HSCT in patients with hematologic malignancies (Fig 1).

Graft-Versus-Host Disease

Graft-versus-host disease is primarily a donor T cell–mediated syndrome whereby T cells in the graft elicit an immune response, resulting in host tissue damage [5]. Hematopoietic stem cell transplantation recipients typically receive conditioning regimens consisting of chemotherapy and/or radiation to eliminate their underlying malignancy and facilitate the engraftment of allogeneic stem cells. However, the conditioning regimen can cause damage to host tissues, triggering the release of proinflammatory cytokines and activating the innate immune system, including host antigen-presenting cells [6]. Donor T cells in the graft interact with activated host antigen-presenting cells, recognize presented host peptides as foreign, and differentiate into cytokine-producing T effector cells. The ensuing proinflammatory cytokine storm recruits other effector cells, such as NK cells and macrophages. This perpetuates the proinflammatory cytokine cascade that is a hallmark of acute GVHD (aGVHD) and results in direct tissue damage, generally to a restricted set of organs (eg, skin, liver, and gastrointestinal tract) [7]. A second phase of GVHD, known as chronic GVHD (cGVHD), tends to have a more delayed presentation in patients, broader organ involvement, and clinical features that bear strong resemblance to autoimmune disorders [8]. Both aGVHD and cGVHD can be characterized as resulting from an imbalance between the effector and regulatory arms of the immune system [9]. Clinical approaches that restore effective immune regulation are, therefore, an attractive treatment strategy for GVHD.

Regulatory T cells are characterized by the coexpression of CD4, high levels of surface CD25, and a master switch transcription factor called forkhead box P3 (Foxp3) that suppresses autoreactive lymphocytes and control innate and adaptive immune responses [10]. As they suppress exuberant immune system activation and promote immunologic tolerance, they have been a focal point of research studies designed to mitigate the severity of GVHD in early-stage clinical trials.

Role of Tregs in Human GVHD

Conflicting results have been published about the role of Tregs in GVHD. Magenau et al [11] showed that aGVHD was associated with a decrease of Tregs frequency in the peripheral blood of allo-HSCT recipients; moreover, several reports demonstrated a decreased frequency of Tregs in the peripheral blood of patients with high clinical grades of aGVHD as compared to patients with lower grade aGVHD [12,13]. Similar results have also been observed in cGVHD, where the frequency of Tregs negatively correlated with disease severity [12,14]. However, not all studies have demonstrated a correlation between reduced Tregs frequency and GVHD severity. Schneider et al [15] observed that cGVHD patients had increased numbers of peripheral blood $CD4^+CD25^+$ Tregs as compared to individuals without cGVHD. This was supported by 2 more recent studies that reported increased peripheral Tregs numbers in transplant recipients that developed cGVHD compared with those with no GVHD [16,17].

The reason for the differences observed in these studies is not entirely clear. For the most part, however, studies have failed to demonstrate that the Tregs frequency and/or absolute numbers predict the occurrence of GVHD; potential reasons include (*a*) sampling of a nonrepresentative compartment (peripheral blood may not reflect gut/skin populations) or (*b*) inadequate sensitivity with current techniques to discriminate host antigen-specific T cells/Tregs, where potentially larger differences might be observed.

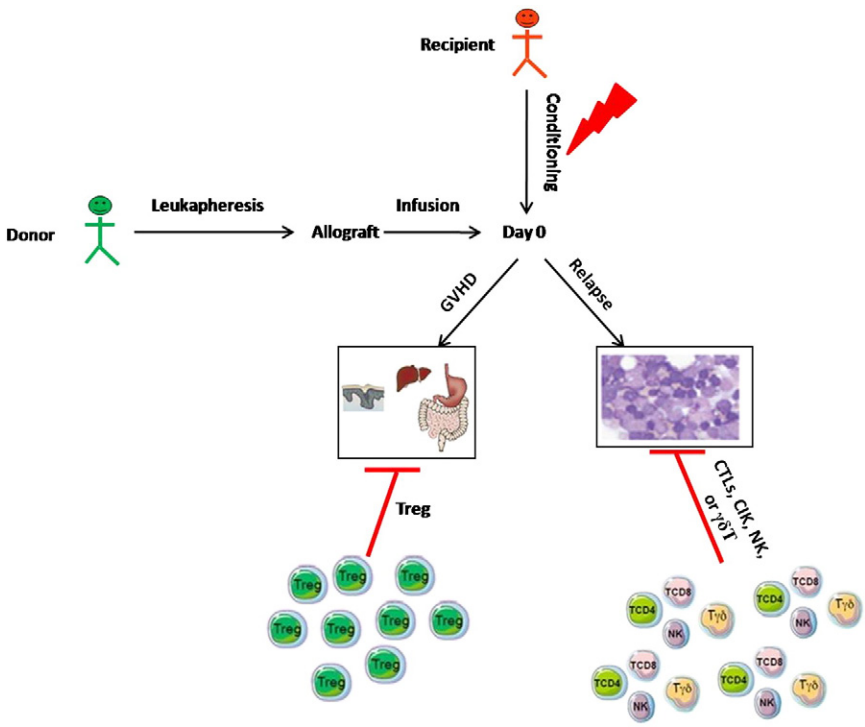

Fig 1. Complications after allo-HSCT such as GVHD and disease relapse can be managed by adoptive immunotherapeutic approaches (eg, Tregs, CTLs, γδ T cells, CIK cells, or NK cells).