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Phase I Clinical Trial of Costimulated, IL-4 Polarized Donor CD4$^+$ T Cells as Augmentation of Allogeneic Hematopoietic Cell Transplantation

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ABSTRACT

The primary objective of this clinical trial was to evaluate the safety, feasibility, and biologic effects of administering costimulated, interleukin (IL)-4 polarized donor CD4$^+$ T cells in the setting of HLA-matched sibling, T cell-replete allogeneic hematopoietic cell transplantation (HCT). Forty-seven subjects with hematologic malignancy received granulocyte colony-stimulating factor-mobilized allogeneic hematopoietic cell transplants and cyclosporine graft-versus-host disease (GVHD) prophylaxis after reduced intensity conditioning. Initial subjects received no additional cells (n = 19); subsequent subjects received additional donor CD4$^+$ T cells generated ex vivo by CD3/CD28 costimulation in medium containing IL-4 and IL-2 (administered day 1 after HCT at 5, 25, or 125 × 10^6 cells/kg). Studies after HCT included measurement of monocyte IL-1α and tumor necrosis factor α, detection of T cells with antitumor specificity, and characterization of T cell cytokine phenotype. The culture method generated donor CD4$^+$ T cells that secreted increased T helper 2 (Th2) cytokines and decreased T helper 1 (Th1) cytokines. Such Th2-like cells were administered without infusional or dose-limiting toxicity. The Th2 cohort had accelerated lymphocyte reconstitution; both cohorts had rapid hematopoietic recovery and alloengraftment. Acute GVHD and overall survival were similar in the Th2 and non-Th2 cohorts. Th2 cell recipients tended to have increased monocyte IL-1α and had increased tumor necrosis factor α secretion. CD8$^+$ T cells with antitumor specificity were observed in Th2 and non-Th2 cohorts. Post-transplantation T cells from Th2 cell recipients secreted IL-4 and IL-10 (Th2 cytokines) and IL-2 and interferon γ (Th1 cytokines). Allograft augmentation with costimulated, IL-4-polarized donor CD4$^+$ T cells resulted in activated Th1, Th2, and inflammatory cytokine pathways without an apparent increase in GVHD.

KEY WORDS

Graft versus host disease • Th2 cells • Tetramers • Cytokines

INTRODUCTION

Allogeneic T lymphocytes mediate graft-versus-leukemia (GVL) effects [1] and initiate graft-versus-host disease (GVHD), which remains the primary complication of allogeneic hematopoietic cell transplantation (HCT) [2]. Immunosuppressive agents used for GVHD prophylaxis generally limit the success of allogeneic HCT to patients with indolent or chemotherapy-sensitive malignancy [3-5]. Use of allogeneic HCT is thus at an immunologic impasse because needs exist to augment antitumor effects and decrease GVHD.

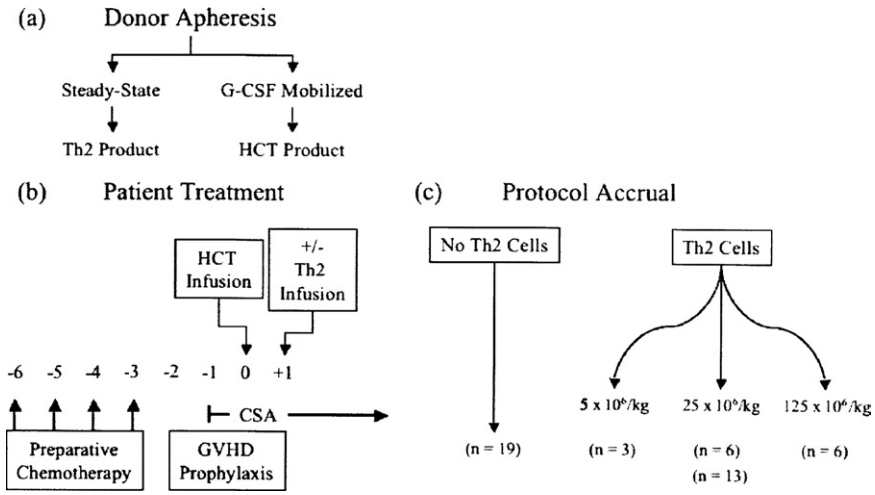

Figure 1. Phase I clinical trial design. A, Donor apheresis. Steady-state apheresis was initially performed for ex vivo generation of the Th2 cell product; subsequently, granulocyte colony-stimulating factor (G-CSF) therapy was started for mobilization of the HCT cell product. Both cell products were cryopreserved. B, Treatment timeline. Subjects underwent induction chemotherapy followed by preparative chemotherapy that consisted of fludarabine (30 mg/m^2 per day) and cyclophosphamide (1200 mg/m^2 per day) on days −6, −5, −4, and −3. GVHD prophylaxis consisted of cyclosporine A (CSA) that was initiated on day −1. The HCT cell product was infused on day 0; Th2 cell infusion occurred on day +1. C, To establish clinical results using a new immunoablative preparative regimen, initial subjects (n = 19) received allogeneic HCT without Th2 cell infusion. Subjects were then sequentially enrolled to receive Th2 cells 5 × 10^6 cells/kg (level 1; n = 3), 25 × 10^6 cells/kg (level 2; n = 6), and 125 × 10^6 cells/kg (level 3; n = 6). The protocol was then amended to allow further subject accrual to dose level 2 to evaluate in a preliminary manner whether Th2 cells might decrease acute GVHD relative to the initial subjects not receiving Th2 cells.

GVHD pathogenesis involves donor interleukin (IL)-2 and interferon γ (IFN-γ) secreting T helper 1 (Th1) cells that promote monocyte IL-1α and tumor necrosis factor α (TNF-α) secretion [6]. Murine T helper 2 (Th2) cells, which secrete IL-4, IL-5, IL-10, and IL-13, can decrease GVHD [7,8]. In humans, Th1/Th2 balance may modulate GVHD, because donor IL-2 and IL-4 secretion was associated with increased and decreased GVHD, respectively [9,10]. As such, Th2 cell graft augmentation represents a new approach to balance GVHD and GVL effects.

To generate Th2 cells, we modified an investigational method of T cell costimulation with anti-CD3/CD28-coated magnetic beads that yields CD4 cells expressing a polyclonal T cell receptor (TCR) repertoire [11]. This method has potential utility in allogeneic hematopoietic stem cell transplantation (HSCT) because antigens accounting for GVHD and GVL effects are incompletely characterized. Anti-CD3/CD28-stimulated T cells, which secrete primarily Th1 cytokines [12], have been evaluated for therapy of human immunodeficiency viral disease [13], lymphoma [14], myeloma [15], leukemia [16], and as donor lymphocyte infusions [17]. In this phase I study, we generated donor Th2 cells through costimulation and expansion in Th2-promoting cytokines (IL-4 and IL-2) [18] and evaluated their safety, feasibility, and biologic effects when administered with T cell-replete allogeneic HCT.

METHODS

Study Design, Accrual

A phase I, 4-arm, sequential study was designed (Figure 1). Initial subjects (n = 19) underwent transplantation without Th2 cells, as previously detailed [19]. Accrual to Th2 treatment arms occurred in a dose-escalation manner at 5, 25, and 125 × 10^6 Th2 cells/kg. The numbers of subjects to be treated were 3 (dose level 1), 3 (dose level 2), and 6 (dose level 3). One dose level 2 subject developed toxicity potentially attributable to Th2 cells (disseminated intravascular coagulopathy); as per protocol design, 3 additional dose level 2 subjects were accrued. Four of 6 subjects receiving dose level 2 did not develop acute GVHD. Following protocol amendment, up to 18 additional subjects (maximum total of 24 subjects) were potentially to have been treated at level 2 to have adequate power to determine in a preliminary manner whether Th2 cells decrease GVHD relative to non-Th2 recipients. After accrual of 13 additional subjects, it was determined that acute GVHD was not decreased; because the study safety endpoint had been met, further accrual was stopped.

Protocol Implementation

The National Cancer Institute (NCI) and University of Pennsylvania institutional review boards and the Food and Drug Administration approved the protocol. All subjects provided informed consent. Eligi-