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ScienceDirect
Transfusion and Apheresis Science 36 (2007) 79–85
TRANSFUSION AND APHERESIS SCIENCE
intl.elsevierhealth.com/journals/tras

The effect of extracorporeal photoimmunotherapy (ECP) on serum TNF-a level in chronic graft versus host disease (GvHD)

Erol Ayyıldız, Önder Arslan *, Pervin Topçuoğlu, Mutlu Arat, Klara Dalva, Ender A. Soydan, Meltem Tol, Osman İlhan

Ankara University, Faculty of Medicine, Department of Hematology, Blood Bank and Apheresis Unit Cebeci, 06590 Ankara, Turkey

Received 6 April 2006; accepted 6 June 2006

Abstract

Graft versus host disease (GvHD) is the most prominent cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (Allo-HCT). Extracorporeal photoimmunotherapy (ECP) is an alternative therapeutic modality in steroid and/or cyclosporin-A refractory GvHD developing after Allo-HCT. The aim of this study was to evaluate whether there was any relation between serum TNF-a levels and the response to ECP in patients with steroid refractory of extensive chronic GvHD. Between March 2001 and August 2003, seven patients (male: 1, female: 6) had ECP for treatment of steroid refractory extensive chronic GvHD. Five age and gender matched healthy volunteers were included in this study as the control group. The age of the patients ranged from 18 to 49 years. All patients were allografted from HLA-idenditical sibling donors. The median number of ECP sessions was 10 (8–36), consisting of two sequential cycles monthly. For measurement of serum TNF-a levels, blood samples were obtained both prior to ECP (basal) and after the first and second in all patients and in five patients after the 10th session. Serum TNF-a levels (Quantakine HS, R&D system, UK) were measured in peripheral venous blood samples by an ELISA method. ECP was given at a median of 5.8 months (1–14 months) after allo-HCT. No complications were seen during or after the ECP procedures. The median time of an ECP session was 183 minutes. The median volume of Uvadex used per session was 4.40 ml (3.61–5.61). The basal mean level of TNF-a was higher in patients than in the control group (2.47 ± 0.83 pg/ml vs. 1.75 ± 0.06, $p = 0.05$). The mean TNF-a levels decreased from 2.47 ± 0.83 pg/ml to 1.77 ± 0.93 pg/ml after the initial session ($p = 0.045$) and from 2.32 ± 0.92 pg/ml to 1.69 ± 0.93 pg/ml after the second day ($p = 0.015$). After completion of the ECP sessions, extensive chronic GvHD recovered in only three patients. In three clinically responsive patients, the TNF-a levels were significantly reduced after both the second and tenth sessions. In contrast, in two patients not responding to ECP therapy, TNF-a levels were increased. In order to report whether these changes in TNF levels is an early predictor for evaluation of the efficacy of ECP in extensive chronic GvHD, TNF-a levels should be studied in a larger series.

Keywords: Tumor necrosis factor (TNF); Extracorporeal photoimmunotherapy (ECP); Graft versus host disease (GvHD)

* Corresponding author. Tel.: +90 312 5957379; fax: +90 312 3097018.
E-mail address: arslan@medicine.ankara.edu.tr (Ö. Arslan).

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doi:10.1016/j.transci.2006.06.007

1. Introduction

After allogeneic hematopoietic stem cell transplantation (allo-HSCT), graft versus host disease (GvHD) develops as a result of the interaction between alloreactive donor T-cells, antigen presenting cells, accessory effector cells and various cytokines released from the donor and host cells [1,2]. GvHD occurs either as an acute (less than 100 days after transplantation) or a chronic (more than 100 days after transplantation) disease and contributes significantly to morbidity and mortality.

Chronic GvHD affects 30–50% of recipients of unmodified HCT and resembles an overlap of various autoimmune diseases [3]. Chronic GvHD may be limited to localized skin involvement and liver dysfunction, or the disease may be more extensive with generalized skin involvement and additional organ involvement. Patients with limited disease may not require treatment; however, those with extensive disease require treatment to decrease the chance of progression to end stage disease. Primary therapy for extensive chronic GvHD includes prednisone and cyclosporine A (CsA) or tacrolimus (FK 506) and/or other immunosuppressive agents such as mycophenolate mofetil. During these conventional immunosuppressive treatments, many patients with chronic GvHD may become refractory, dependent or suffer from significant toxicities. Alternative approaches for prevention and treatment of GvHD are constantly being sought.

The incidence of chronic GvHD has been gradually increasing, especially in patients conditioned with a reduced intensive regimen and infusion of peripheral blood progenitor cells as a stem cell source allografted from a HLA matched unrelated- or mismatched related donor [4–7].

TNF-a is a polypeptide of 157 aminoacid residues [8]. TNF-a is produced by neurophils, activated T- and B-lymphocytes, NK cells, LAK cells, astrocytes, endothelial cells, smooth muscle cells and some transformed cells [9]. The conditioning regimens of allo-HCT lead to damage of the recipient's tissues and results in release of some cytokines such as TNF-a, IL-1 and IL-6, which increase the consecutive expression of HLA and other critical adhesion molecules and contribute to increased activation of donor T-cells present in the donor hematopoietic cell inoculums [10]. Since these inflammatory cytokines, especially TNF-a, cause damage to the epithelial cells, the risk of GvHD might be increased [11].

Photopheresis, termed as extracorporeal photoimmunotherapy (ECP), is a new therapeutic method for GvHD [12]. ECP has been mainly described as a process in which peripheral blood mononuclear cells obtained from the patient, following treatment by 8-methoxypsorelan (8-MOP) and irradiated by ultraviolet-A, are returned to the same patient [12,13]. Known mechanisms of action of ECP are: (1) the photoactive liquid psoralen (UVADEX, Therakos Inc.) intercalates itself within the DNA strands of cells; (2) upon activation by UV-A light, psoralen undergoes a conformational change and causes intra-strand and inter-strand photo-adducts-cross-linking the DNA and prohibiting transcription from occurring; and (3) the combination of psoralen and UV-A light eventually leads to apoptosis of the white cells, and these apoptotic cells are re-infused into the patient [14].

Photopheresis has exhibited promising activity in a number of T-cell mediated or immune-mediated inflammatory diseases such as cutaneous T-cell lymphoma, solid organ transplant rejection, scleroderma, atopic dermatitis and, of particular interest, graft versus host disease [15]. In this study we aimed to determine whether the serum TNF-a level is an early predictive factor for expressing ECP efficacy in patients with extensive chronic GvHD.

2. Patients and method

2.1. Patients

Between March 2001 and August 2003, seven patients with chronic GvHD, who were steroid refractory or dependent and given ECP therapy at Ankara University, Department of Hematology, and Hemapheresis Unit, were included in this study. All patients and the healthy volunteers gave written consent (the consent form was approved by the institutional review board). Their ages varied from 18 to 49 years (six females and one male). All patients were allografted from an HLA-matched sibling donor. As a stem cell source, peripheral blood progenitor cells were infused to five patients or bone marrow for two patients. The patients' characteristics are reported in Table 1.

A physician experienced for the complications after allo-HSCT, evaluated all patients at 2nd and 4th weeks. Also, a specialist in pulmonary disease examined the patients who had broncholitis obliterans and evaluated their respiratory function tests and high-resolution computerized tomography.