Immunology Summit-2013
OMICS Group Conferences
Accelerating Scientific Discovery
2nd International Conference on
Clinical & Cellular Immunology
October 15-17, 2013 Hampton Inn Tropicana, Las Vegas, USA

Inactivation of human white blood cells in platelet products after pathogen reduction technology (PRT) treatment in comparison to gamma irradiation

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Abstract

Functional leukocytes in blood components may be responsible for a number of adverse transfusion effects, including transfusion-associated graft versus host disease (TA-GvHD), alloimmunization and alloimmune platelet refractoriness. TA-GvHD occurs when functional lymphocytes are transfused into a patient who is unable to mount an immune response to the human leukocyte antigen (HLA) due to HLA-compatibility or immunosuppression. More than $8x10^4$ viable leukocytes are required to cause TA-GvHD and this disease occurs infrequently, but is in >90% cases fatal. Death occurs approximately 2-3 weeks after transfusion.

Alloantibodies against HLA-antigens on donor leukocytes and platelets are the major cause of refractoriness to platelet transfusions in patients receiving repeated blood transfusions. Attempts to reduce these undesirable effects have included leukoreduction filters and gamma-irradiation. Studies have shown that exposure of platelet concentrates to riboflavin and light (Mirasol® PRT) causes irreparable modifications of nucleic acids that result in inactivation of a wide range of pathogens as well as inhibition of the immunological responses mediated by leukocytes present in platelet concentrates.

The effect of the Mirasol PRT treatment of blood products on WBC function was tested and compared to gamma-irradiation. PRT treatment and gamma-irradiation reduced the ability of the T-cells to proliferate by similar degrees as evidenced by a ≥6 log reduction in the limiting dilution assay (LDA). Both treatments inhibited the ability of WBCs to proliferate in response to any stimuli tested. After PRT treatment, but not after gamma-irradiation, WBCs were unable to present antigen and stimulate proliferation in allogeneic responder cells. In addition, PRT-treated T-cells could not be activated by PMA, whereas cells after exposure to 25 Gy gamma-irradiation upregulated surface expression of CD69. PRT treatment resulted in a significantly reduced secretion of pro-inflammatory cytokines (TNF-α, IL-1□, IL-6, IL-8) in response to LPS and of IFN-□□, IL-2, IL-10 and TNF-□□□ in response to anti-CD3/28 antibodies. In contrast, cytokines released by gamma-irradiated WBCs were not significantly different than untreated controls. In addition, Dr. Fast showed that xenogeneic GvHD in animals injected with PRT-treated WBCs was prevented, as evidenced by lack of GvHD development, human cell engraftment, antibody production, and increase in human cytokine levels (Fast et al, 2013 Transfusion; 53: 373-81, see Table 1).

Rachael Jackman and colleagues at Blood Systems Research Institute have suggested that the inability of PRT treated WBCs to act as antigen presenting cells may be due to defective cell-cell adhesion between the antigen presenting and allogeneic responder cells (Jackman et al. 2009 Transfusion;49: 2686-2699). If a PRT method can prevent leukocytes from inducing proliferation in allogeneic cells, a resultant hypothesis is that this treatment may prevent alloimmunization and platelet refractoriness. This hypothesis was investigated in an animal model by Asano *et al*. Results from these rat studies suggest that PRT treatment may reduce or eliminate alloantibody generation and alloantibody-mediated cardiac graft rejection, observed as a result of transfusion of leukocytes (Table 2).

These in vitro results demonstrate that Mirasol PRT treatment is more effective than gamma irradiation at abrogating selected WBC immune functions.

Biography

I obtained my PhD in 1999 from University of Würzburg, Germany in collaboration with the Department of Immunology at National Jewish Health. After working for 5 years as a Research Associate in the field of HIV-mediated immune dysfunction with focus on T-cell signaling, I went to work for Proneuron, a company developing a novel cell therapy to treat spinal cord injuries. In 2006 I joined Terumo BCT (formerly Gambro BCT or CaridianBCT) as a Senior Scientist in the blood component business segment. Since 2012 I have been leading the Scientific Affairs group.