TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 7
Number 2 *Spring 2014*

1-1-2014

Current Research of Extracorporeal Photopheresis and Future Applications

Chaim Lederer
Touro College

Current Research of Extracorporeal Photopheresis and Future Applications

Chaim Lederer

Abstract

Photopheresis, also known as Extracorporeal Photopheresis (ECP) is making inroads in treatment of previously untreatable diseases. As the medical world has delved deeper into, Although the mechanisms of photopheresis are largely unknown, increasingly detailed studies have proven its efficacy. The lack of side effects has made photopheresis an ideal option for patients. The treatment is also versatile enough that it can be used as a mono-therapy or as a supplement to other traditional therapies. The use of photopheresis has been proven successful in the treatment of cutaneous T-cell lymphoma (CTCL) and graft-versus-host disease (GvHD), and is currently being administered for immune system disorders, bone marrow, or stem cell implantation, liver, heart, or lung transplants (where there is fear of rejection) and any

Introduction

Research in the field of Extracorporeal Photopheresis (ECP) commenced in 1982. Richard Edelson, MD, a Professor at Columbia University, had been experimenting with a therapy he invented as an alternative treatment for untreatable cancers. After many years of research, he achieved an astonishing clinical success in the treatment of two patients with extensive cutaneous T-cell lymphoma (CTCL). Previously, in the 1970's, Dr. Edelson noted that removing circulating cancer cells from patients with Sezary Syndrome (SS), a form of CTCL, by way of repetitive Leukapheresis, resulted in a temporary improvement in their skin disease. Leukapheresis is a procedure that removes abnormal white blood cells from the blood. It is a form of apheresis, which is the process of removing one particular constant from the blood and returning the rest to circulation. In the 1980's, Dr. Edelson collaborated with Therakos, a Johnson and Johnson company, to design a device to accomplish Leukapheresis while simultaneously exposing a small amount of the patients' white blood cells to Methoxsalen, a light sensitizing drug, and ultra violet (UVa) light to activate the medication.

Immunity: Background Information

The immune system consists of differentiated hematopoietic cells that are created from bone marrow hematopoietic stem cells (HSC). HSCs separate into various types of blood components such as erythroid cells, platelets, myeloid cells (such as neutrophils, basophils, eosinophils, monocytes), mast cells, natural killer cells, dendritic cells, natural killer T cells, thymus derived cells (T cells), and B cells depending on the environment and stimuli (Lensch, 2012). These immune cells arrange host protection by responding to foreign antigens after the cells mature. However, a proper maintenance of cellular and molecular balance is crucial for these immune responses to proceed. Once this delicate balance is askew, normal immunity is disrupted and diseases with increased susceptibility to infection arises.

Within the immune system, the Dendritic cells (DC) are antigen-presenting cells. The DCs, also known as accessory cells, play an integral role in both inborn immunity and adaptive immunity. The cells link inborn and adaptive immunity by activating B and T-cells through the presentation of antigens on their cell surfaces (Novak, et al, 2010). When B-cells are triggered by DCs, an immune response consisting of secretion of antigen specific antibodies occurs. Simultaneously, DCs activate CD4+ helper and CD8+ T-cells that define and stimulate T-cell responses specific to each antigen (Banchereau, Steinman, 1998). Depending on the nature of the antigen, different CD4+ T-helper (Th) responses such as Th-1, Th-2, Th-17, and T-regulation can occur. Th-cells also secrete cytokines that promote cell interactions with additional cells, which

Chiam Lederer graduated in May 2014 with a B.S. in Biology.

are then dispatched to the infected site. For example, the Th-1 response is mediated by CD4+ helper T-cells and CD8+ T-5 cells that secrete IFN-γ, IL-2, and IL-12 to fight against viruses. The CD4+ helper cells then "help" to invoke a cytotoxic attack against the virus, mainly through CD8+ cytotoxic T-cells (Steinman, Hemmi, 2006) (Kadowaki, 2007) .

Located in the immune system, T-regulatory cells (T-regs) regulate a wide variety of immune cells such as CD4+, CD8+, B-cells, natural killer T-cells, and antigen presenting cells (APC) both in vitro (artificial environment) and in vivo (natural environment). These cells make up 5-10% of the total agranulocytic cells found in the body's blood (Sakaguchi, 2008). They have the distinct ability to regulate reactions in the immune system, preventing immune diseases such as allergies and autoimmunity. T-regs have often been recognized as the cause for failure of cancer vaccines. On the other hand, T-regs also have potential use for patients with irregular immune systems. In autoimmune patients, an increase in T-regs may be an ideal method of treatment since their immune system is compromised and these cells could help regulate it. Similarly, the removal of T-regulatory cells may assist in increasing a cytotoxic response to tumor antigens.

Cutaneous T-cell Lymphoma (CTCL)

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of non-Hodgkin's peripheral T-cell lymphomas that mainly affect the skin. Two of the most common forms of CTCL are Mycosis Fungoides (MF) and Sézary Sydrome (SS). They are distinguished by malfunctioning CD4+ T-cells and impaired immunity. Together they encompass approximately 70% of all CTCL cases. About 1,500 new cases of MF/SS are reported yearly, and there are currently 16,000-20,000 individuals living in the United States with MF/SS (Criscione, Weinstock, 2007). CTCLs are incurable and thought to arise from uncontrolled reproduction and accumulation of atypical mature helper, memory clonal T-lymphocytes (Vonderheid, Bernengo, 2003).

Sézary Syndrome (SS)

Discovered and introduced by Albert Sézary in 1938, Sézary Syndrome (SS) is a form of leukemia consisting of cells with cerebriform shaped nuclei, itching, exfoliative dermatitis, and adenopathy (inflammation of the lymph nodes). Patients with SS do not have a good prognosis; there is an average survival rate of only 3 years (Scarisbrick, et al, 2001). SS patients have been found to have a high rate of Staph colonization. Secondary and hospital acquired infections, most often from Staphylococcus aureus (Staph) sepsis due to an impaired immune system, breaks in the skin and use of catheters are particularly fatal in SS patients. The cause of SS is unknown and the diagnosis is very difficult due to its similarities to other skin ailments. It was originally believed that SS was derived from MF. However, MF and SS can be differentiated since MF cells are effector memory T-cells and SS cells are central memory T-cells. With Sèzary cells, they are also found in both the blood and skin with CD4+ T cells lacking the expression of CD-26 or CD-7. (Campbell, et al, 2010)

Graft-versus-Host Disease (GvHD)

Graft-versus-host disease (GvHD) is an immune system disorder that limits the use of stem cell and bone marrow transplant therapies. The donor immune cells used in the transplant recognize host cells as being foreign, based on human leukocyte antigen (HLA) mismatch. The donor cells mount an immunological attack, resulting in damage to organs including the skin, gut, liver, eyes, or lungs.

There are two types of GVHD, acute GVHD and chronic GVHD. Symptoms occurring within 100 days post-transplant are described as acute GVHD and any occurrence of symptoms beyond 100 days are characterized as chronic GVHD. An analysis of acute GVHD showed that amongst the patients affected 81% had skin involvement, 54% had gastrointestinal involvement, and 50% had liver involvement (Martin, et al, 1990). Candidates for transplant therapies have a plethora of ailments which can lead to incrased numbers of antigen presenting cells resulting from damages produced by a multitude of factors such as underlying disease and its treatmentvia chemotherapy, radiation, and infections. In order to prepare the host's body for transplantation, the patient has to undergo a procedure called total body irradiation. Total body irradiation is used to suppress the immune system, thus preventing the patient's immune system from destroying implanted cells that are foreign to the body. During this procedure,

inflammatory cytokines such as IL-1 and tumor necrosis factors (TNF) are secreted from the patient's tissues. Cytokines, which can potentially cause damage to the gastrointestinal tract via endothelial apoptosis, may increase the severity of GvHD if the microbial products such as bacteria attack the blood system. Activation of the immune system or tolerance by the body is controlled by APC's that are activated by these secretions (Roncarolo, et al, 2001).

In the cells there is a major histocompatibililty complex (MHC). The MHC is a set of molecules on the surface of the cells which facilitates the interactions of leukocytes (WBCs). CD4+ and CD8+ T-cells, and cytokines are the main disease facilitators. In every individual, the MHC takes on its own unique genetic coding. One of the primary functions of the MHC is the recognition of foreign antigens invading the immune system. Since the MHC is highly polymorphic, it has the ability to recognize countless types of antigens. It then binds peptide fragments taken from the pathogens and displays them on the cell surface for recognition by the T-cells. The MHC presents the antigens to the T-cell receptor (TCR), and the T-cells are activated or deactivated via an interaction between the TCR and the MHC. In the case of GvHD, everything is awry because the grafted T-cells fail to recognize the MHC proteins on host cells. Due to the MHC mismatch, the graft T-cells attack the host cells thinking they are foreign even though they are non-antigenic. Thus, the MHC mismatch contributes to the disrupted normal immunity leading to GVHD.

Extracorporeal Photopheresis (ECP)

Extracorporeal Photopheresis is a pioneering treatment with minimal side effects, which improves the quality of life, and has increased the survival rates for persons with select incurable diseases. Based on clinical trials, the procedure was approved by the FDA for treatment of erythrodermic Leukemic-CTCL (L-CTCL) (Edelson, et al, 1987). At the time, response rates between 54% and 66% had been reported in L-CTCL patients with about 10% complete responders (Jiang, et al, 1999) (Crovetti, et al, 2000). This opened up a new world of possibilities in the treatment of cancers. Most cancer treatments come with a large amount of side effects along with the possibility of a cure. This treatment had the potential of accomplishing the latter, with almost no risk of side effects.

In the ECP procedure that was created by the Therakos company, blood is drawn from the arm or a central catheter, and a very small amount (5x109) of the patients white blood cells (3-5%) are separated and collected for irradiation or apheresis. The blood is centrifuged to separate the leukocyte enriched blood portion from the red blood cells in plasma. The rest of the blood is automatically returned to the bloodstream. The collected white blood cells are then treated with a medicine called Methoxsalen/Uvadex. The drug is activated when it is exposed to ultra-violet (UV) light. The medicated white blood cells are exposed to UVa light, with a strength of 1.5 J/cm^2. The function of the medication is to covalently bind and cross-link DNA, leading to apoptosis of treated cells. These cells are now known as Methoxsalen treated buffy coat cells. The buffy coat cells are then re-infused back into the patient . so that they can cause an immune response. In the body, the spleen and the liver now pick up the Methoxsalen treated white blood cells. The day after ECP treatment, the treated cells undergo apoptosis. Even though the mechanism is not understood, these cells are phagocytized by antigen presenting cells (APC) that are causing disorder in the body. It is theorized that the phagocytosis causes a regulation of immune responses by altering the APC function. The APC's now become immunological tolerant inducing or tolerogenic to the immune system. The phagocytosis causes a decrease in the secretion of pro-inflammatory cytokines and effector T-cells. Additionally, it causes an increase in anti-inflammatory cytokines such as TGF-beta and IL-10. This process and reaction causes a boost in the activation and stimulation of T-regulatory cells which in turn leads to a healthy regeneration and rebalancing of the T-cells and other immune cells in the body. Additionally, blood that has been irradiated halts lymphocytes from causing harm to patients who have compromised immune systems. ECP does not cause any known harm to the body, and the blood does not become radioactive or toxic.

Since there was some understanding as to how ECP was able to achieve these positive results, it brought about the possibility of expanding its usage for other severe diseases. These diseases include: multiple sclerosis

(MS), systemic sclerosis, Crohn's disease, rheumatoid arthritis, type-1-diabetes, and autoimmune diseases such as lupus. Trials have also begun in cases of whole transplanted organ rejection. In CTCL patients, ECP has shown the successful destruction of malignant T-cells via apoptosis and the differentiation of monocytes into effective antigen presenting dendritic cells. These two outcomes concurrently lead to a decrease of the tumor load and initiation of antitumoral immune response. (Garban, et al, 2012).

Studies

Studies have shown the efficacy of ECP treatment in patients with early-stage mycosis fungoides (MF). The studies were conducted with ECP as a mono-therapy and as a supplement to the traditional cancer therapies. The patients underwent treatment of ECP for two days every four weeks over a time span of six months. Those that had a partial response continued the treatment of ECP for the full six months and those without an initial response added oral bexarotene and/or interferon α. These studies produced astonishingly positive results.

Participants included nineteen patients with early-stage MF (7 men, 12 women; 16 white, 3 African American) with an average age of 63.5 years (range, 46-85 years). 42% of the participants responded to the ECP by itself with an average amount of 12 ECP sessions over 12 months (8/19; including 7 partial response, 1 complete response). Seven of the patients with stabilized MF at 3 months received additional bexarotene treatment (3/5; 1 complete response) or were administered bexarotene plus interferon α (1/2), and 57% (4/7) responded to the updated treatment. Side effects were limited to those expected with standard chemotherapy treatment. The effects included nausea, vomiting, and diarrhea.

The studies proved that ECP is effective for patients with early-stage MF alone or in combination with drugs and included improved quality of life. It has shown a response of as high as 42% with ECP treatment alone (Talpur, et al, 2011)

Another study was on the efficacy of ECP on steroid-dependent acute GVHD. A complete resolution was attained in 82% of patients with skin involvement, 61% with liver involvement, and 61% with gut involvement. These patients received ECP on 2 consecutive days every one to two weeks, until there was a noticeable response and continued every two to four weeks until it reached a maximum response. The next stage conducted was a study of the relationship of mortality and survival. The 4-year survival rate for those in whom acute GVHD had a complete response was 59% (Kumar, 2011).

When ECP was first introduced into the medical world, it was only proven to work on CTCL and GvHD. Due to the success, the research community continued looking to see which other ailments the treatment could be applied to. This has become a worldwide concerted effort in attempt to make headway in previously incurable diseases and clinical trials have begun on the effect of ECP on many different unrelated or atypical diseases..

Another case where the curative effects of ECP can be observed is through studies involving patients afflicted with Crohn's disease, who are incapable of responding to alternative treatments such as immune-suppressants and/or anti-TNF therapies. After twelve sequential weeks of treatment, the success of the individual's results were evaluated based on the patient's decrease in their Crohn's Disease Activity Index (CDAI) of less than or equal to 100 points, or the remission which can be characterized by an index of less than 150 points. From the 28 patients that participated in the study, half successfully responded to the treatment with 13 subjects reacting at week 6, and 7 of them obtaining remission after the 12-week interval. From the 12 patients who chose to advance with a 12-week extension study, 9 continued to effectively respond to the treatment. Through their study, clinicians were capable in discerning ECP as a productive means in which patients with Crohn's disease were able to attain desirable results (Abreu et. al.. 2009).

Conclusion

Beginning with the initial successes in the 1980's, extracorporeal photophersis has been a medical breakthrough in a field where there rarely is a cure found with limited or no side effects. The difficulty of understanding how it achieves its results has not been a deterrent to further expansion of its usage. Today, ECP is at the forefront of clinical trials bringing hope to many with lim-

ited options or where the cure is sometimes just as deadly as the disease, as is the case in chemotherapy and radiation treatments. With its versatility, ECP becomes an additional option even for patients already using other therapies. Trials have produced extremely promising results for diseases with little or no hope. To date, ECP has only been approved for treatment in CTCL and GvHD, but current trials are expanding its usage. ECP has promising potential to be the cure of the future pertaining to immune system related diseases.

References

Abreu MT, Tirpitz Cv, Hardi R, Kaatz M, Assche G v, et. al., (2009). Extracorporeal photopheresis for the treatment of refractory Crohn's disease: Results of an open-label pilot study. Inflammatory Bowel Diseases, 15:6, 829-836.

Banchereau J, Steinman RM, (1998). Dendritic cells and the control of immunity.

Nature, 392, 245-252.

Campbell JJ, Clark RA, Watanabe R, Kupper TS, (2010). Sezary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. Blood, 116, 767-771.

Criscione VD, Weinstock MA, (2007). Incidence of cutaneous T-cell lymphoma in the United States. Archives of Dermatology, 143, 854-859

Crovetti G, Carabelli A, Berti E, Guizzardi M, Fossati S, De Filippo C, Bertani E, (2000). Photopheresis in cutaneous T-cell lymphoma: five-year experience. Int J Artif Organs, 23, 55-62.

Edelson R, Berger C, Gasparro F, Jegasothy B, Heald P, Wintroub B, Vonderheid E, Knobler R, Wolff K, Plewig G, (1987). Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. Preliminary results. New England Journal of Medicine, 316, 297-303.

Garban F, Carras S, Drillat P, Jacob MC, Fabre B, Callanan M, Courby S, Makowski C, Cahn JY, Gressin R, (2012). Extracorporeal photopheresis as a curative treatment strategy in non epidermotropic T-cell lymphoma and large granular lymphocyte leukemia. Retrieved from the web 12/24/2013. Ann Oncol. http://annonc.oxfordjournals.org/content/early/2012/03/15/annonc.mds014.full

Greinix HT, (2009). The Role of Extracorporeal Photopheresis in Graft-vs-Host Disease. Asia-Pacific Journal of Oncology and Hematology, 3, 1-5.

Jiang SB, Dietz SB, Kim M, Lim HW, (1999). Extracorporeal photochemotherapy for cutaneous T-cell lymphoma: a 9.7-year experience. Photodermatol Photoimmunol Photomed, 15, 161-165.

Kadowaki N, (2007). Dendritic cells: a conductor of T cell differentiation. Allergology International, 56, 193-199.

Kumar A, (2011). Using Extracorporeal Photopheresis in the Treatment of Graft-Versus-Host Disease. Retrieved from the web 1/19/14. http://www.onclive.com/publications/obtn/2011/june-2011/using-extracorporeal-photopheresis-in-the-treatment-of-graft-versus-host-disease/2

Lensch, M Wiliiam, (2012). An evolving model of hematopoietic stem cell functional identity. Stem Cell Reviews and Reports, 8, 551-560.

Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, Appelbaum FR, Beatty PG, Doney K, McDonald GB, Sanders JE, (1990). A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. Blood, 76, 1464-1472.

Ni X, Zhang C, Talpur R, Duvic M. Resistance to activation-induced cell death and bystander cytotoxicity via the Fas/Fas ligand pathway are implicated in the pathogenesis of cutaneous T cell lymphomas. J Invest Dermatol 2005;124:741-50.

Novak N, Koch S, Allam JP, Bieber T., (2010). Dendritic cells: bridging innate and adaptive immunity in atopic dermatitis. The Journal of Allergy and Clinical Immunology, 125, 50-59.

Roncarolo MG, Levings MK, Traversari C, (2001). Differentiation of T regulatory cells by immature dendritic cells. The Journal of Experimental Medicine, 193, F5-9.

Sakaguchi S, Yamaguchi T, Nomura T, Ono M, (2008). Regulatory T cells and immune tolerance. Cell, 133, 775-787.

Scarisbrick JJ, Whittaker S, Evans AV, Fraser-Andrews EA, Child FJ, Dean A, Russell-Jones R, (2001). Prognostic significance of tumor burden in the blood of patients with erythrodermic primary cutaneous T-cell lymphoma. Blood., 97, 624-630.

Steinman RM, Hemmi H, (2006). Dendritic cells: translating innate to adaptive immunity. Current Topics in Microbiology and Immunology, 311, 17-58.

Talpur R, Demierre MF, Geskin L, Baron E, Pugliese S, Eubank K, Zic JA, Miller DR, Tharp M, Bohjanen K, Duvic M, (2011). Multicenter photopheresis intervention trial in early-stage mycosis fungoides. Clin Lymphoma Myeloma Leuk, 11(2), 219-27.

Vonderheid EC, Bernengo MG, (2003). The Sezary syndrome: hematologic criteria. Hematology/Oncology Clinics of North America, 17, 1367-1389.