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Review

A concise review on extracorporeal photochemotherapy: Where we began and where we are now and where are we going!

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ABSTRACT

Currently, more than 1080 peer-reviewed papers are displayed on PubMed when initiating a search for therapeutic indications and mechanisms of action of extracorporeal photochemotherapy (ECP). This concise review focuses mainly on some prevalent and traditional treatment-resistant disorders with an emphasis on immunologic complications emerging from stem cell and solid organ transplantation.

Contents

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1. Introduction

The main objective of this short review is to foster an interest in the biological and clinical advantages of extracorporeal photochemotherapy, a relatively new and distinctive therapeutic approach. We hope the readers will be stimulated to undertake and participate in research studies to further our current understanding of the immune mechanisms, procedure variables and prognostic indicators that underlie the efficacy of ECP.

2. Historical aspects

Extracorporeal photochemotherapy (ECP, photopheresis) is a method of treatment in which the mononuclear cells of the patient are ex vivo exposed to photo activated 8-methoxypsoralen (8MOP), and subsequently reinfused back to the patient. In 1988, the US Food and Drug Administration approved extracorporeal photochemotherapy (ECP) for treatment of cutaneous Tcell lymphoma (CTCL) initiating "de facto" the era of modern photobiology and photomedicine. A year before that, Edelson and colleagues published in the New England Journal of Medicine (NEJM) a paper entitled "Treatment of cutaneous T-Cell Lymphoma by Extracorporeal Photochemotherapy" that was considered a milestone in the treatment of CTCL [1]. Despite its current limited use in lymphoma, ECP has gained credence as a therapy for various T-cell mediated diseases. In France, Georges Andreu, Farhad Heshmati and Annette Bussel set up an original technical variant so-called French method of ECP, which consisted of collecting a highly enriched mononuclear cells (MNC) by the continuous flow cell separator (Spectra, COBE Lab), transferring the collected cells into a UV-A permeable bag (Macopharma), adding 8-metoxypsoralen directly to the bag of and irradiating the collected MNC with a well-defined and controlled dose of UV-A with UV-Matic irradiator (Vilbert-Lourmat).

In 1998, the "French School" represented by Becherel et al. demonstrated the effectiveness of ECP in the field of autoimmune diseases by successfully treating erosive oral lichen planus, a premalignant inflammatory disease widening the potential application of this therapeutic approach to other T-cell disorders besides CTCL [2]. At the same time Barr and Dall'Amico explored the feasibility of ECP in prevention of cardiac transplant rejection. They demonstrated its efficacy in a randomized prospective multi-center study encompassing 60 consecutive recipients of primary cardiac transplants [3].

Concurrently, Irena Sniecinski at the City of Hope developed a different methodological approach by combining the two known ECP techniques. She collected MNC using the continuous flow cell separator and irradiated the collected cells with the Johnson & Johnson device. Most importantly, she perceived the possibility of employing ECP in the field of severe immunological disorders, specifically in the treatment of acute and chronic graft versus host disease (GvHD), a major cause of morbidity and mortality in allogeneic hematopoietic stem cell transplantation (HSCT) [4–6].

This abbreviated tour of ECP evolution, which originated with the singular purpose of curing an advanced hematologic malignancy, unexpectedly progressed to modulate immune responses, and eventually became a large-scale unique cell therapy. It calls to mind a famous album of the seventies, "What a long strange trip it's been" [7].

3. Mechanism of action and immunological effects

Basic questions that have occupied researcher in ECP include: "What autoimmune and malignant diseases benefit from ECP and is there a common mechanism to explain its action?" The answer is not yet conclusive, but some significant strides have been made.

Mechanism of action of ECP still remains elusive despite the large number of studies performed through the years and the development of several animal models with different immunological and autoimmune diseases [8–10]. The combination of 8-MOP and UV-A with a wavelength ranging from 329 to 400 nm affects many cellular components even if the principal target remains DNA. The final result of cell irradiation by UV-A is DNA cross-linking with pyrimidine bases, binding to cytosolic proteins, cell membrane damage with some antigenic modifications and finally the apoptotic cell death [11]. For many years, the direct cytotoxicity was believed to be the main mechanism responsible for antitumor effect of ECP in CTCL, but it was found totally inadequate to explain the antineoplastic effect produced by a very low number (less than 10%) of effector cells [12]. However, the activation of cytotoxic CD8 + T-cells through an increase of expression of class I major histocompatibility complex (MHC) after ECP may explain the efficient elimination of the malignant T-cell-clones [13].

After stimulation in the presence of antigen presenting cells, activated T cells differentiate into one of several lineages. In addition to the effector cell lineages, T cells can differentiate into regulatory cells (Tregs) that down regulate harmful immune reaction. Tregs are deficient in both animal models and patients with acute graft versus host disease, and Treg cell therapies have been proposed as a treatment for GvHD [14–17]. The induction of Tregs through the secretion of inflammatory cytokines is one of the most invoked mechanisms of the immune-modulatory effect of ECP [18]. Biagi et al. demonstrated in a clinical study a significant rise of Treg cell numbers (from 8.9% to 29.1%) in the peripheral blood of GvHD patients after at least six ECP treatments [19]. The mechanism by which this happens remains unclear. ECP-induced Tregs displayed cell-to-cell contact-dependent immune suppression against effector T-cells.

An alternative mechanism involving the tolerogenic effect generated by infusion of apoptotic monocytes and other antigen presenting cells has been proposed [20,21]. It has been noted that circulating monocytes come into contact with the plastic surface of the extracorporeal device, which can induce differentiation of monocytes to immature dendritic cells [22,23]. These cells are implied in maintaining and ensuring peripheral tolerance. The use of mesenchymal dendritic cells (MSC) has been shown to have a similar efficacy in clinical trials and animal models of acute GvHD [24,25]. After infusion MSC become apoptotic and break down into immunosuppressive exosomic particles. A similar mechanism may occur in ECP.