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Review

The role of extracorporeal photopheresis in the treatment of cutaneous T-cell lymphomas

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ABSTRACT

Extracorporeal photochemotherapy (ECP) is an effective treatment modality for patients with erythrodermic myocosis fungoides (MF) and Sezary syndrome (SS). During ECP, a fraction of peripheral blood mononuclear cells is collected, incubated ex-vivo with methoxypsoralen, UVA irradiated, and finally reinfused to the patient. Although the mechanism of action of ECP is not well established, clinical and laboratory observations support the hypothesis of a vaccination-like effect. ECP induces apoptosis of normal and neoplastic lymphocytes, while enhancing differentiation of monocytes towards immature dendritic cells (imDCs), followed by engulfment of apoptotic bodies. After reinfusion, imDCs undergo maturation and antigenic peptides from the neoplastic cells are expressed on the surface of DCs. Mature DCs travel to lymph nodes and activate cytotoxic T-cell clones with specificity against tumor antigens. Disease control is mediated through cytotoxic T-lymphocytes with tumor specificity. The efficacy and excellent safety profile of ECP has been shown in a large number of retrospective trials. Previous studies showed that monotherapy with ECP produces an overall response rate of approximately 60%, while clinical data support that ECP is much more effective when combined with other immune modulating agents such as interferons or retinoids, or when used as consolidation treatment after total skin electron beam irradiation. However, only a proportion of patients actually respond to ECP and parameters predictive of response need to be discovered. A patient with a high probability of response to ECP must fulfill all of the following criteria: (1) SS or erythrodermic MF, (2) presence of neoplastic cells in peripheral blood, and (3) early disease onset. Despite the fact that ECP has been established as a standard treatment modality, no prospective randomized study has been conducted so far, to the authors' knowledge. Considering the high cost of the procedure, the role of ECP in the treatment of SS/MF needs to be clarified via well designed multicenter prospective randomized trials.

Contents

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1. Introduction

The development of extracorporeal photochemotherapy (ECP) emerged as a result of persistent research efforts to understand the beneficial effects of UV radiation for the treatment of skin diseases [1]. It has been known from the 1950s, that topical application of psoralen on the surface of skin lesions and the subsequent exposure to sunlight had significant therapeutic impact in patients suffering from psoriasis or cutaneous lymphoma. ECP was introduced into clinical practice by Edelson et al. by the end of 1980s, for the treatment of patients with primary cutaneous T-cell lymphomas (CTCL) and was accompanied by very encouraging results [2]. It was subsequently applied to other diseases or conditions, such as the rejection of transplanted solid organs and the treatment of graft versus host disease (GVHD) following allogeneic hematopoietic stem cell transplantation. In this chapter we will refer to the application of ECP in the treatment of cutaneous lymphomas and more specifically to the following subgroups: myocosis fungoides (MF) and Sezary syndrome (SS). The effect of ECP to a patient with SS can be seen in Fig. 1. ECP has no place in the treatment of other primary cutaneous or systemic lymphomas except the aforementioned.

2. ECP procedure

ECP requires the collection of peripheral blood mononuclear cells, 8-methoxypsoralen (8-MOP) and UVA irradiation. 8-MOP is widespread in nature, it belongs to the group of furocoumarins and it is a biological inert substance that has no effect on human cells. Following systemic administration or in vitro incubation with eukaryotic cells, 8-MOP enters the cell nucleus and binds to thymidine bases, without causing any further biochemical changes. Following exposure to UVA, 8-MOP molecule becomes activated, forming crosslinks between the two DNA strands, resulting in inhibition of replication and transcription of the genetic material. This leads to the activation of cellular apoptosis.

ECP is carried out in the following stages [1,3], also shown in Fig. 2:

(1) Collection of the mononuclear cell layer from patient's peripheral blood (buffy coat fraction) using a special leukapheresis machinery. The total collected buffy coat quantity corresponds to 5–10% of the total peripheral blood mononuclear cells.
(2) Ex-vivo buffy coat incubation with 8-MOP.
(3) Ex-vivo UVA irradiation of the cell mixture (buffy coat and 8-MOP).
(4) Reinfusion of irradiated cells into the patient.

ECP is performed with a special apheresis machine using a disposable closed system. The procedure is performed ex-vivo and requires good venous access, thus many patients require a central venous catheter insertion. Two ECP sessions on two consecutive days constitute one treatment cycle. The interval between each cycle of treatment should not exceed 1 month. Most centers suggest two cycles per month, for the first 3 months, and then one cycle per month [3]. There is no absolute agreement for the duration of treatment. Usually treatment is stopped if there is no therapeutic response following a 6–12 month treatment. If there is a response, treatment is carried out until optimal response is achieved. Furthermore, there is no agreement to whether a maintenance treatment should be administered when maximum response is achieved. The side effects of the treatment are mainly those related to central venous catheter insertion, rather than ones related to the procedure itself.

3. Mechanism of action

The mechanism of action of ECP it is not yet fully elucidated and it is a subject of ongoing research. Existing data is briefly described in the following paragraphs. It has been

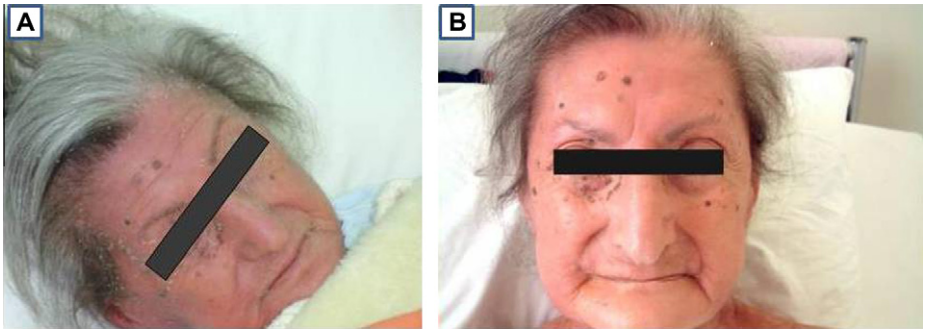

Fig. 1. Patient with Sezary syndrome. (A) Before, and (B) after treatment with extracorporeal photopheresis.