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Review

Extra corporeal photochemotherapy in steroid refractory graft versus host disease: A review of guidelines and recommendations

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ABSTRACT

Regardless of remarkable progresses in prevention and treatment approaches, graft versus host disease (GVHD) remains a major impediment for successful allogeneic hematopoietic stem cells transplantation (HSCT) and leads to morbidity and mortality in transplanted patients. Corticosteroids are the standard therapy for GVHD; however, a great number of patients will not respond sufficiently and others will be significantly affected by adverse effects of steroids. Extracorporeal photochemotherapy (ECP), as one of the numerous second line therapies, through modulation of immune cells may improves GVHD affected organ function in steroid-refractory forms. Considering to widespread utilization of ECP as a therapeutic strategy, we performed review on current literature of ECP, regarding the treatment strategies, monitoring protocols and technical aspects in chronic and acute GVHD.

Contents

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1. Introduction

Extracorporeal photochemotherapy (ECP) is defined as a leukapheresis-based therapy [1] consisting of three main steps: leukapheresis; photo activation using 8-methoxypsoralen (8-MOP) and ultraviolet A (UVA) and reinfusion of buffy coat.

During ECP, patient's whole blood is processed by an automated machine. First noticeable point during the procedure is blood harvesting via a suitable peripheral vein or using a central catheter. Then, mononuclear cell (MNC) isolation from other components of blood such as red blood cells (RBCs) and plasma is achieved by centrifugation. Afterwards, a mixture of MNCs and 8-MOP are exposed to UVA light in a distinct plastic chamber in order to cell photo modification, finally, these MNC are re-infused to the patient [2]. ECP is performed through 2 different methods: on-line and off-line techniques. In "on-line" system (Therakos, Exton, PA, USA), 8-MOP is directly added to the buffy-coat/plasma blood fraction and the mixture circulates in the plastic chamber before UVA radiation and re-infusion. On the other hand, in the "off-line" system the product is collected by a cell separator and then transferred to a UV bag and after addition of 8-MOP, MNC are irradiated by UVA (Macogenic, Macopharma, Toucoin, France) and then re-infused to patients [3,4]. Although ECP is not considered as a routine treatment, it is commonly used for severe refractory GVHD. However this method was firstly introduced for cutaneous T cell lymphoma (CTCL) in clinical settings [5–7], it has also been proved efficient in other severe and therapy resistant conditions such as GVHD following allogeneic stem cell transplantation, systemic sclerosis, prevention and treatment of rejection in solid organ transplantation, Crohn's disease and various other diseases [7,8]. Moreover, the immunomodulatory action of ECP through several reputed mechanisms is proved [7,9,10]. Considering this potential, ECP is now used in many transplant institutions for treatment of patients with acute and chronic GVHD [11]. Despite the widely uses of ECP as a therapeutic method, it may be difficult for some clinicians to achieve a consensus on patient selection criteria, monitoring approaches, assessment protocols and treatment schedules among different hematopoietic transplantation centers for GVHD treatment. Thus, this paper aims to review the current literature on ECP with particular emphasis on cited problems.

2. Methodology

Following extracted guideline was obtained through a literature review of those papers focusing on GVHD treatment using ECP published on PubMed and Scopus. The literature appraised in the current guidelines was collected from most recent published data. The reviewed guidelines presented here is an up to date extract of the indications, treatment schedules, monitoring protocols and technical aspects of ECP for adults and pediatric GVHD. The aim of this review was to answer the following questions regarding GVHD:

The aim of this review was to answer the following questions regarding GVHD:

1. Which patients should be considered for ECP treatment?
2. What are the contra-indications for ECP?
3. What is the optimal duration and schedule of treatment?
4. How should the therapeutic efficacy be assessed?
5. How should the ECP quality be monitored?

3. Results

3.1. ECP guideline for chronic GVHD (cGVHD) in adults and pediatric

3.1.1. Patient selection and inclusion criteria

ECP is recommended (grade 1B) as the second-line treatment for skin, oral and liver manifestations of GVHD [12,13]. So far, different recommendation grades have been emerged for ECP therapy for cGVHD. The grade 1B is introduced to those situations where the benefits of ECP therapy are strongly recommended but there is moderate quality evidence. Alternatively, patients with contra-indications for standard first-line corticosteroid therapy are considered to receive ECP treatment [13–15].

According to the studies it seems that ECP has no immunosuppressive effects, drug interactions. This method is a safe immunotherapy with the lowest risk of disease relapse, secondary infection and malignancy. ECP is an effective treatment for GVHD but graft-versus-leukemia (GVL) effect seems not to be impaired by ECP [16]. After HSCT or donor lymphocyte infusion (DLI), patients with cGVHD who are primarily affected in at least one of the following organs: skin, mucosal membranes (such as mouth and eye disease) and liver, could benefit from this treatment. The treatment begins with confirming cGVHD through compatible histology analysis of the affected organ biopsy by a pathologist [17,18]. GVHD which is affecting other organs is not precluded by ECP treatment and should be monitored for possible responses. ECP is mostly and successfully used for mentioned situations and there is inadequate evidence to recommend it in other pathologies [19,20]. Patients are advised to receive ECP as the second or third line of treatment with the following feature: [3,21,22]:

- **Steroid refractory:** minimal or absence of response to 1 mg/kg prednisolone for at least 4 weeks.
- **Steroid dependency:** inability to reduce prednisolone to <10 mg or the equivalent amount of similar steroids daily without flare of GVHD.

According to the studies, the median (range) interval between HSCT and beginning of ECP treatment of cGvHD, 193 days have been reported [17,22].

3.1.2. Exclusion criteria

3.1.2.1. Hematological contraindications.

- Patients with severe anemia or thrombocytopenia are not suitable candidates for ECP unless they receive adequate transfusion support of irradiated and leukoreduced blood components. The target goals for hemoglobin (Hb) and platelet are to reach more than 8 g/dL and more than 20×10^9/L, respectively [3].
- ECP is contra-indicated in the case of WBC count $<1 \times 10^9$/L unless WBC count increased by G-CSF [23]. So far, no study has considered the minimum mononuclear cells (MNC) count for ECP therapy. Although no evidence strongly supports a threshold for MNC count, most clinicians delay ECP treatment until a MNC count of at least 200×10^6 cells/L is reached [3,22].
- Positive history of shifted antithrombotic treatment to an alternative anticoagulation therapy [3,24].