Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

TRANSFUSION
CLINIQUE ET BIOLOGIQUE

Transfusion Clinique et Biologique xxx (2017) xxx–xxx

Original article

Extracorporeal photochemotherapy in mycosis fungoides

Photochimiothérapie extracorporelle dans les mycoses fongiques

E. Atilla [a,*], P.A. Atilla [a], S.C. Bozdag [a], M.K. Yuksel [a], S.K. Toprak [a], P. Topcuoglu [a], B.N. Akay [b], H. Sanli [b], H. Akan [a], T. Demirer [a], M. Beksac [a], O. Arslan [a], M. Ozcan [a], G. Gurman [a], O. Ilhan [a]

[a] *Department of Hematology & BMT Unit, School of Medicine, Ankara University, Cebeci Hospital, 06590 Ankara, Turkey*
[b] *Department of Dermatology, Ankara University School of Medicine, 06100 Ankara, Turkey*

Abstract

Objectives. – Extracorporeal photo-chemotherapy (ECP, photopheresis) is an approved treatment modality for mycosis fungoides (MF). Our aim is to present our ECP data for MF.
Methods. – We retrospectively evaluated 50 MF patients who received ECP for clinical activity, toxicity, and response and outcome rates, and we compared these with combination therapies.
Results. – The overall response rate (ORR) was 42% (21/50), while the median time to response was 11 months (range, 3–48 months). Ten of the responders (48%) had 3 or more treatment lines prior to ECP. Eight patients (16%) had adverse events related to ECP. The overall survival (OS) of 50 patients was 72 months (range, 3–211). There was no statistically significant difference in the OS in early-stage vs late-stage patients (77 vs 69 months, $P = 0.077$). The stage 3 and 4 patients received an average of 31 cycles compared to 55 cycles in stage 1 and 2 patients ($P = 0.006$). The increased extent of ECP was not correlated with the response. Combined treatment with ECP significantly improved the OS (84 months vs 62 months, $P = 0.005$).
Discussion. – A low frequency of side effects and improved OS observed in combination therapy makes ECP a favorable option for treating MF.

Keywords: Extracorporeal photo-chemotherapy; Mycosis fungoides; Combination therapy

Résumé

Objectifs. – La photochimiothérapie extracorporelle (ECP, photophérèse) est une modalité de traitement approuvée pour le mycosis fongoïde (MF). Notre objectif est de présenter nos données ECP pour le MF.
Méthodes. – Nous avons évalué rétrospectivement 50 patients MF qui ont reçu une ECP pour l'activité clinique, la toxicité, les taux de réponse et le résultat, et nous les avons comparés avec des thérapies combinées.
Résultats. – Le taux de réponse global (ORR) était de 42 % (21/50), alors que le délai moyen de réponse était de 11 mois (intervalle, 3–48 mois). Dix des personnes qui ont répondu (48 %) disposaient de 3 lignes de traitement ou plus avant l'ECP. Huit patients (16 %) avaient des effets indésirables liés à l'ECP. La survie globale (OS) de 50 patients était de 72 mois (3–211). Il n'y avait pas de différence statistiquement significative de l'OS chez les patients atteints par stade avancé ou tardif (77 contre 69 mois, $p = 0{,}077$). Les patients de stade 3 et 4 ont reçu une moyenne de 31 cycles comparativement à 55 cycles pour le stade 1 et 2 ($p = 0{,}006$). L'étendue accrue de l'ECP n'a pas été corrélée avec la réponse. Le traitement combiné avec ECP a considérablement amélioré la survie globale (84 mois contre 62 mois, $p = 0{,}005$).
Discussion. – Une faible fréquence des effets secondaires et une amélioration de l'OS font de l'ECP une option favorable pour le traitement du MF.

Mots clés : Photochimiothérapie extracorporelle ; Mycosis fongoïde ; Thérapie combinée

* Corresponding author.
E-mail address: erdenatilla@gmail.com (E. Atilla).

http://dx.doi.org/10.1016/j.tracli.2017.05.001
1246-7820/

1. Introduction

Primary cutaneous T-cell lymphoma (CTCL) is the second-most common extranodal non-Hodgkin lymphoma, with a yearly incidence of 0.45 per 100,000 [1]. In the WHO-EORTC classification, the CTCL group consists of mycosis fungoides (MF), and its variants, including Sezary syndrome (SS), primary cutaneous CD30+ lymphoproliferative disorders, and less common diseases (adult T-cell leukemia, extranodal NK/T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and primary cutaneous peripheral T-cell lymphoma) [2]. The treatment options depend on the stage of MF. In early phases, skin-directed therapies, including topical steroids and phototherapy, are mainly administered. In advanced-phase disease, biologic therapies, such as interferon or bexarotene, together with electron-beam radiotherapy and chemotherapy, are the treatments of choice [3].

Extracorporeal photo-chemotherapy (ECP, or photopheresis) is a treatment method that includes the ex vivo exposition of mononuclear cells to photo-activated 8-methoxypsoralen (8MOP) and reinfusion to the patient [4]. Although only 5–10% of the mononuclear cells are influenced in the procedure, the treatment causes long-lasting immunomodulatory effects by inducing tolerance of regulatory T cells. ECP has been reported to be effective for a wide variety of diseases, such as CTCL, autoimmune diseases, graft versus host disease and organ graft rejection. Many studies have been conducted to determine the mechanism of action of ECP, but it has still not been well defined.

The US Food and Drug Administration approved ECP for treating CTCL in 1988 after Edelson et al. published a manuscript in the *New England Journal of Medicine* entitled "Treatment of Cutaneous T-Cell Lymphoma by Extracorporeal Photo-chemotherapy" [5]. CTCL is associated with an imbalance in the Th1/Th2 immune response, which in turn is associated with an increased release of IL-4 and IL-5, reduced activity of NK cells and reduced cytotoxicity of CD-8 positive T cells. Di Renzo et al. demonstrated an increase in CD 36 positive monocytes and a change in the cytokine reaction profile of peripheral blood lymphocytes in patients with early-stage CTCL (stage IB) undergoing ECP for 1 year. ECP was observed to restore the Th1/Th2 balance [6].

Edelson et al. published a meta-analysis of 19 studies in more than 400 CTCL patients in all stages with an overall response rate (ORR) of around 56%, with ECP employed either as a monotherapy or in combination with different agents [7]. The response rates were higher in patients with circulating clonal CD4+/CD7− Sezary cells [8]. Several studies have found an ORR ranging from 42 to 80% and complete response rates from 0% to 30%. This variation arose due to different study designs, stages of disease, prior treatments received, and ECP protocols used. Since the aim of the study clarify the role of ECP in CTCL, we retrospectively evaluated all our patients that diagnosed with any stage CTCL and received ECP alone or in combination as a treatment and analyzed the clinical activity, toxicity, response rates as well as outcome.

2. Patients and methods

This retrospective observational cohort study included 50 MF patients between 1998 and 2015 who were diagnosed and followed at the Ankara University Department of Dermatology and Hematology Clinics. The patients were staged according to the modified ISCL/EORTC classification [9]. For response evaluation, the Global Response Score was determined [10]. The patients' retrospective data were collected using electronic clinical records. All the informed consents were obtained prior to participation. The results were evaluated by SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows®, Version 20.0. Armonk, NY: IBM Corp).

The extracorporeal photopheresis treatment was administered by a trained nursing staff under medical supervision using Uva Pit devices (Uva Pit Med Tech Solutions, Cadolzburg, Germany) system. Informed consents were obtained in each application. Central venous catheters were inserted in 10 patients (20%) without appropriate peripheral access. The initial recommended schedule was one cycle (two consecutive days) every 2 weeks for the first 3 months, then once monthly or every 3 weeks. The treatment continued for at least 6 months. The patients were evaluated in every 3 months. Patients who did not respond to ECP after the recommended waiting period of at least 6 months were considered for combination therapies.

3. Results

The median age of the participants was 55 (range, 25–79). The patients in the study were mostly male (86% vs 7%). The frequency of stages at diagnosis were as follows:

- 17 patients (34%) Stage 1–2;
- 33 patients (66%) Stage 3–4.

First and second line treatments are detailed in Table 1. ECP was the first line treatment only in 2 patients (4%). Twenty five patients (50%) received > 3 lines of treatment prior to ECP. Treatments prior to ECP included topical retinoids

Table 1
First and second line treatments of patients.

	n = 50 (%)
First line treatments	
PUVA	22 (44%)
Interferon	14 (28%)
Topical retinoid	5 (10%)
NBUVB	4 (8%)
Methotrexate	3 (6%)
ECP	2 (4%)
Second line treatments	
IFN	20 (40%)
PUVA	18 (36%)
Methotrexate	7 (14%)
Topical retinoid	3 (6%)
CHOP	1 (2%)
NBUVB	1 (2%)

Please cite this article in press as: Atilla E, et al. Extracorporeal photochemotherapy in mycosis fungoides. Transfusion Clinique et Biologique (2017), http://dx.doi.org/10.1016/j.tracli.2017.05.001