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Management of cutaneous T-Cell lymphoma patients with extracorporeal photopheresis. The hellenic experience

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ABSTRACT

Extracorporeal photopheresis (ECP) is an established therapy for cutaneous T-cell lymphoma (CTCL). The objective of this study was to further explore the clinical efficacy of ECP combined with immunomodulatory agents.

Eighteen patients with histologically proven CTCL were followed-up after therapy with ECP, mainly combined with interferon-α or bexarotene.

A total of 61% of patients responded to therapy (n = 11; CR: 5, PR: 6). Median survival was 51 months, progression free survival was 28 months and response duration was 29 ± 23.9 months.

ECP combined therapy was highly effective or had a palliative effect in CTCL resistant to previous treatments.

1. Introduction

Cutaneous T-cell lymphoma (CTCL) comprises a heterogeneous group of rare lymphoproliferative disorders, characterized by clonal T-cell invasion of the skin and whose most common forms include mycosis fungoides (MF) and its leukemic variant, Sézary syndrome (SS) [1]. First described by Edelson in 1987, extracorporeal photopheresis (ECP), is an established treatment for CTCL, mostly used as a first-line therapy in erythrodermic MF and SS patients, while ECP's efficacy is also proven for the treatment of other T-cell mediated conditions, like chronic graft versus host disease (cGVHD) and solid organ transplant rejection [2–4]. Response rates of CTCL patients to ECP have been shown to range widely between different studies, from 43% to 100%, a fact attributable to variable patient selection, duration of treatment and administration of adjuvant therapies [5]. Regarding patient selection, studies primarily include patients with advanced-stage disease. However, a few studies have suggested a beneficial role of ECP in early-stage CTCL patients, especially when other therapeutic modalities have failed [6]. ECP has been applied either as monotherapy or in combination with other agents. Although data about the efficacy of combination therapies are limited, the addition of adjunct regimens to ECP has been shown to result in higher response rates and appears to be more effective than ECP alone [7–10]. We present the experience of three Greek Institutions with ECP, combined with other modalities, mainly interferon-α (IFN-α) and bexarotene, with regard to patients outcome and the impact on survival.

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2. Materials and methods

2.1. Patients

We studied 18 patients, 10 males and 8 females with a median age 55 years (range 27–79) with histologically proven CTCL, who started ECP between May 2003 and January 2010 and were followed up until May 2011 (median follow up: 34 ± 25 months). Stages were defined according to the ISCL/EORTC revised staging and classification system [11]. Patient population included 12 MF and 6 SS patients. Regarding disease stage, 13 patients had advanced MF or SS (stages IIB–IV) and 5 patients had early stage CTCL (stages IA, IB, and IIA). Seventeen patients had received other treatments without remission before initiating ECP. All erythrodermic and SS patients complained of severe pruritus. T-cell clonality in the skin biopsies and peripheral blood was assessed by T-cell receptor rearrangement (TCR) by the polymerase chain reaction (PCR) analysis.

2.2. Treatment

All patients underwent ECP using the UVAR® XTS™ system (Therakos, Exton, PA, USA) according to standard procedures [12]. Each cycle of ECP consisted of two daily procedures during two consecutive days. Treatment schedule was as follows: one cycle of ECP every week for 1 month, followed by one cycle of ECP every 2 weeks for another 2 months, and then one cycle of ECP every month. All patients were considered as evaluable, after receiving 3 months of treatment or more.

All patients except one, received ECP combined with adjuvant therapy (ECP + IFN-α: 6, ECP + bexarotene: 8, ECP + IFN-α + bexarotene: 1, ECP + pentostatin: 1, ECP + Denileukin diftitox: (1). Patients' characteristics, treatment and clinical outcome are shown in Table 1.

2.3. Evaluation of response

Response assessment was based on clinical evaluation of skin disease, computed tomography (CT) scan evaluation regarding lymph node and visceral disease and blood immunophenotypic analysis, in relation to patients' pretreatment staging. Complete response (CR) was defined as the disappearance of all evidence of disease for at least 4 weeks, partial response (PR) as a $\geqslant$50% tumor regression and at least a 50% reduction in Sézary cell counts for a minimum of 4 weeks, without the appearance of new lesions. Progressive disease (PD) was defined as an increase of more than 25% in skin disease, the appearance of new lesions and/or lymphadenopathy and stable disease (SD) was defined as no change in the skin evaluation or other evidence of progression [13].

2.4. Statistical analysis

Progression free survival (PFS) was calculated as the time from the beginning of ECP to either the first date, which met criteria of progression, or death as a result of any cause. Response duration was calculated as the time from the date when criteria for response (CR or PR) were first met until the date of relapse or progression. Statistical differences were evaluated by the χ^2 test. Progression free survival and overall survival were analyzed according to the Kaplan–Meier product-limit method.

3. Results

3.1. Response rate

Overall, 11 patients responded to treatment (CR: 5 and PR: 6; response rate: 61%) and the remaining showed stable disease or progression. Pruritus subsided in the responding patients after two weeks of ECP treatment. Considered by diagnosis, 6 out of 12 MF patients responded to treatment, compared to 5 out of 6 patients in the SS group. Moreover, 9 out of 13 patients (62%) with advanced CTCL (stages IIB–IVB) responded, compared to 2 out of 5 (40%) patients with early stage disease (stages IA–IIA). Regarding the main treatment groups, 3 out of 6 patients responded to ECP + IFN-α therapy, compared to 6 out of 8 patients in the ECP + bexarotene group. The above distributions did not reach statistical significance ($P > 0.05$). T-cell clonality was investigated in the skin biopsies of all patients and in the blood of 15 patients. Blood TCR rearrangement was detected in 12 patients of the same size as in the skin. Seven blood TCR(+) patients and 3 TCR(−) patients responded to treatment. CTCL had been diagnosed less than two years before the application of ECP in 9 patients and more than two years before the application of ECP in the other 9 patients. The difference in response rates was statistically significant, as in the first group 8 patients responded to treatment compared to 3 in the second group ($P < 0.05$) (Fig. 1).

3.2. Survival analysis

The PFS for all patients was 28 months and the response duration for the responding patients was 29 ± 23.9 months (Fig. 2). The PFS for patients receiving ECP + bexarotene was 28 months and for those receiving ECP + IFN-α was 40 months, a difference however not being statistically significant (Fig. 3). The median survival was 51 months.

4. Discussion

CTCL constitutes a heterogeneous group of diseases characterized by the malignant proliferation of clonally derived T lymphocytes which predominately bear a CD4 + T-helper/inducer phenotype. CTCL patients present with a variety of cutaneous lesions and often complain of pruritus which is resistant to conventional supportive treatments. Although there is not a standard treatment for CTCL, skin oriented therapies are recommended for early stages, whereas combination of various immunomodulating agents and/or chemotherapy are reserved for advanced or refractory disease [14]. ECP is a leukapheresis-based therapy, based on extracorporeal treatment of peripheral blood mononuclear cells with 8-methoxypsoralen (8-MOP) and irradiation with ultraviolet A (UVA) light, followed by