Extracorporeal Photopheresis as a Treatment for Patients with Cutaneous T-Cell Lymphoma: Real-World Data at a Reference Cancer Center in Colombia.

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Abstract

Background: Extracorporeal photopheresis (ECP) is an innovative therapy. It excels in its clinical benefit and low toxicity for patients with cutaneous T-cell lymphomas (CTCL) in advanced stages. ECP is available at the “Instituto Nacional de Cancerología” (National Cancer Institute) in Bogotá, Colombia since 2016. This being currently the only device available in the country. The objective of this study is: to generate real-world evidence by describing the results of patients treated with ECP through a descriptive analysis of population characteristics, showcase the results of the treatment in terms of response and survival, and associated complications regarding said treatment. This is a case-series descriptive study, which included patients diagnosed with erythrodermic MF and SS treated with extracorporeal photopheresis following institutional protocols.

Results: 616 ECP sessions were performed in 17 patients. Overall response rate (ORR) was obtained in sixteen patients (64,7%), with a partial response (PR) in nine patients (52,9%), and complete response (CR) in two patients (11.8%). Response rates improved when combined with adjunctive therapies. The median mSWAT reduction was 98 points and the median VASP reduction was 4 points on the analogous visual scale. Median survival for the entire group measured from the onset of treatment until death was not reached (95% CI: 859-NA). The 12-month survival probability was 82% (95% CI: 66-100%). Complications occurred in 2% of performed sessions, most related to difficulties in the venous access.

Conclusion: ECP should be considered as first-line therapy for erythrodermic MF/SS based not only on its efficiency and excellent side effect profile but also on the significant improvement of the symptoms.

Abbreviations
CTCL: Cutaneous T-cell lymphomas
SS: Sézary Syndrome
MF: Mycosis Fungoides
ECP: Extracorporeal photopheresis
ORR: Overall response rate
PR: Partial response
CR: Complete response
mSWAT: Severity Weighted Assessment Tool
VASP: Visual Analogal Scale Pruritus
EORTC: European Organization for Cancer Research and Treatment
TCR: T-cell receptor
SD: Standard deviation
IQR: Interquartile range
CHOP: chemotherapy combination with cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone
IFN: Interferon alfa
GM-CSF: Granulocyte-macrophage colony-stimulating factor

Keywords

Cutaneous T-cell lymphoma, mycosis fungoides, sézary syndrome, extracorporeal photopheresis, real-world use.

Background

Extracorporeal photopheresis (ECP) was described in 1987 as a potential therapy for patients with cutaneous T-cell lymphomas (CTCL) in advanced stages [1]. In 1988, the FDA approved extracorporeal photopheresis for the treatment of Sézary Syndrome (SS) and erythrodermic Mycosis Fungoides (MF) [1].

ECP is a therapeutic method by which the patient's blood is obtained through a peripheral mean, such as a vein, to isolate the leukocytes from the plasma and non-nucleated cells (platelets and erythrocytes)- this process is known as apheresis. Through special devices, these leukocytes are exposed to a photosensitizing agent (8-methoxy psoralen) to be subsequently subjected to UV-A radiation (329-400nm) and reinfused into the patient [2].

The effect produced by UV-A radiation within the psoralen-exposed DNA, is a crosslinking of the pyrimidine bases, therefore leading the cell to apoptosis [3]. Despite its excellent safety profile and efficacy, the exact mechanism of action of ECP is still under exploration. Based on clinical observations, it is believed to induce an immune response to the malignant T cell clone [1].

Cutaneous lymphomas are a heterogeneous group of Non-Hodgkin lymphomas. With a global incidence of 10.3 per million[6] people annually it represents 19% of extranodal lymphomas [4]. Cutaneous T-cell lymphomas, (which are the most frequent type of lymphoma) account for 75-80% of all cutaneous lymphomas [5].

Mycosis fungoides (MF) is the most frequent variant of CTCL (60%), with an estimated incidence of 5.6 per million people [4-6]. It is staged according to the extent of skin involved (patches, plaques, or tumors). Also the nodal, blood, and visceral compromise [7]. Sézary syndrome (SS) is a rare leukemic form of CTCL, with an estimated incidence of 0.1 per million people in the USA [8]. SS is traditionally defined as a triad of a very itchy erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cell clones with cerebriform nuclei (Sézary cells) in the skin, lymph nodes, and peripheral blood [5].

MF and SS are classified according to the TNMB of the International Society for Cutaneous Lymphomas (ISCL) and the group of cutaneous lymphomas of the European Organization for Cancer Research and Treatment (EORTC) [9]. In this classification, cutaneous lymphomas are divided into two large groups: initial stages (IA, IB, IIA) and advanced stages (IIB, IIIA, IIIB, IVA, IVB).
From stage IIIA (erythroderma), the median survival ranges from 1.4 to 4.7 years. Disease-associated survival ranges from 18% to 45% at 5 years and the risk of disease progression ranges from 53% to 82% at 5 years [10]. Regarding SS, the prognosis is substandard, with a 5-year survival rate of 24% [11].

Globally, there are marked differences related to the therapeutic approaches. Mainly, given the low prevalence of the disease and the scarce evidence available. [12].
The results of the treatment with systemic chemotherapy are unsatisfactory, with low response rates and high toxicity [14, 15]. This treatment option is usually reserved for patients with refractory disease. On their own targeted therapies have an ORR (Overall Response Rate) ranging from 30 to 67%. Furthermore, complete responses do not exceed 41% [13].

Currently, no clinical trials are showing the efficiency of ECP as monotherapy in the treatment of MF/SS. Nonetheless, international organizations propose it as the first-second treatment in advanced stages of the disease.
Edelson et al. reported a response rate of 73% in its original publication[1]. Since then, several case series and retrospective studies have been published confirming the efficiency of ECP. The effectiveness has been seen especially in

patients with erythrodermic MF and SS, displaying response rates of around 60% [16].

Since 2016, the *Instituto Nacional de Cancerología* (National Cancer Institute), holds the only available ECP equipment in the country.
To our knowledge, there is currently no data of studies made with Latin-American populations, moreover, the results of EPC in our target population are unknown. To date, 17 patients diagnosed with erythrodermic mycosis fungoides and Sézary Syndrome have been treated. In a prospective register of the patients treated using EPC, there is a record of more than 600 sessions.
The objective of this study is: to generate real-world evidence, describing the results of patients treated with ECP in our country through a descriptive analysis of the population characteristics, the results of the treatment in terms of response and survival, and the complications associated with said treatment. Additionally, the operational characteristics of apheresis procedures will be described.

In this manner, an interest in the biological and clinical advantages of EPC, and its usage in other clinical scenarios will be fomented.

Methods

Study design

The study at hand is a Case-series descriptive study.

This study included patients that exceeded 18 years of age and were diagnosed with erythrodermic MF and SS further treated with extracorporeal photopheresis, following the established institutional protocols. The treatment consisted of two sessions on consecutive days, every two weeks for at least three months. This was followed by two sessions on consecutive days, every four weeks in the THERAKOS™ CELLEX™ Photopheresis System (Therakos, Exton, PA, U.S.A.). Patients who received at least one apheresis session between October 1st, 2016 and April 30th, 2020 were registered consecutively. The inclusion criteria of the participants were: the patient must be more than 18 years of age, a confirmed diagnosis of MF or SS, the patient must have complete data in the clinical chart regarding the response to treatment, and patients under follow-up at the National Cancer Institute.
The information was taken from the digital medical records and the data of each apheresis procedure performed. Variables included: sociodemographic information (date of birth, sex, affiliation, education, and origin), clinical and treatment information (date of diagnosis, date of onset of extracorporeal photopheresis, response to extracorporeal photopheresis, date of death or last contact with the patient and overall survival).

Statistical analysis

Descriptive analysis was performed to observe the frequency of presentation of the variables under study. It was not intended to establish any kind of statistical inference. Measurements were calculated depending on the type of variable. For the definition of the sociodemographic, clinical-pathological characteristics, and characterization of the treatment, quantitative and qualitative variables were analyzed.
By building tables of frequency distribution nominal and ordinal variables were described by frequencies and percentages. Continuous quantitative variables were described by mean and standard deviation if they meet the normality criteria. Otherwise, they were described by the median and the limits of the interquartile range.
The estimation of global and event-free survival was calculated using the Kaplan-Meier limit product method.
All the information was handled completely anonymously, coding the identification data of the patients and assigning each one a unique registration number that would identify them throughout the study.
Descriptive statistics, survival analysis, and univariate and multivariate analysis were performed in R version 4.02 and STATA version 16.

Ethical Considerations

This study has been designed in coherence with the ethical guidelines and principles for research in human beings. Explicitly, the demands of international documents such as the Declaration of Helsinki and the Belmont Report were fully embraced throughout the study. National documents such as resolution 8430 of 1993 were also used as a guideline. **This study is considered** risk-free research and has been approved by the Institutional Review Board.

Results

Description of Study subjects

Seventeen patients were included, of which ten (58.8%) were male. The median age was 49 years (32-72 IQR 22), being 60.5 years in men and 43 years in women. This difference was statistically significant (p value= 0.019, Mann-Whitney U test). Nine patients (52.9%) had Sézary Syndrome, eight patients (47.1%) had Mycosis fungoides. Six patients (35.3%) had foliculotropic mycosis fungoides, and two patients (11.8%) had hyperpigmented (lichenoid) mycosis fungoides. Distribution of diagnosis by sex is presented in Table 1.

Immunophenotype was CD4+ in fifteen cases (88,2%) and CD8+ only in two cases (11.8%).
Other population characteristics are presented in Table 2.

Initial clinical presentation

Stage information before starting ECP treatment was available in all patients. Eight patients (47.05%) were in stage III and four patients (23.53%) were in stage IV.
A total of 16 patients (94%) were classified as T4 (erythroderma), at the time of the beginning of treatment with ECP. One patient was classified as T2. A young patient with a diagnosis of hyperpigmented MF for more than 10 years, in whom multiple topical and systemic treatments were administered with the persistence of symptoms. The staging data and TNMB distribution is presented in Figure 1.

The detection of Sézary cells was performed by morphological and immunohistochemical analysis. The average number of circulating Sézary cells was 15.62 (SD 20.91). Differences in the number of circulating cells per stage were identified.
These differences were statistically significant (ANOVA F 6.0054, p-value= 0.0085). The difference was found to be significant between stage IVB and IB patients (p-value 0.004, Tukey's test), but there was no difference in any other group. This data is displayed in Figure 2.

T-cell receptor (TCR) gene rearrangements were available in only a limited number of patients. Blood samples were available in five patients (29.4%), being positive in four of them (23.5%). In skin biopsy samples, it was performed in nine patients (52.9%), being positive in six of them (35.3%). Results are presented in table 3.

Previous treatments

Of the seventeen patients, sixteen (94.11%) received skin-directed therapies. The median number of skin-directed therapies was two (0-3, IQR=1). Sixteen patients (94.11%) received topical corticosteroids. Twelve patients (70.58%) received PUVA, only one patient (5.88%) received UVB, and no patients received topical retinoid treatment.

All patients received systemic therapy. The average number of systemic lines before the start of ECP was 2.47 (SD: 1.17). Ten patients (58.82%) received *interferon*, seven patients (41.17%) received *methotrexate*. six patients (35.29%) received CHOP chemotherapy, five patients (29.41%) received *liposomal doxorubicin*, four patients (23.52%) received *vorinostat*, four patients (23.52%) received *pralatrexate*, and seven patients (41.17%) received other treatment. Results are presented in Figure 3.

Nine patients (52.94%) received systemic therapy associated with ECP; five patients (29.41%) received *methotrexate*, three patients (17.64) received *interferon*, one patient (5.88%) received *vorinostat*, and two patients (11.76) received another treatment.

ECP therapy results
In total, 616 extracorporeal photopheresis sessions were performed on 17 patients. The median number of sessions performed per patient was 38 (2-77, IQR: 75) (average 36.2). Figure 4 shows the number of sessions received per patient.

The mean duration of the procedure for the whole group was 2.12 hours (SD: 0.39). The average duration of the procedure through the central venous line was 1.47 hours and through the peripheral venous line was 2.18 hours. The mean treatment volume was 161 ml (SD: 32). The mean photoactivation time was 26.5 min (SD: 6.8). The mean photosensitizing agent volume was 2.78 ml (SD: 0.54). Adverse reactions occurred in 2% of the performed sessions (12 sessions), of which, the most frequent complication was related to difficulties in venous access (10 sessions), followed by technical failure (1 session) and fever (1 session). The characteristics of the sessions discriminated by patient are presented in Table 4.

The median time to the onset of treatment from diagnosis was 359 days (3-2395, IQR 636).

The median mSWAT (modified Severity Weighted Assessment Tool - method of choice for assessing skin tumor burden in both mycosis fungoides and Sézary syndrome) before ECP treatment was 178 (70-400 IQR: 100). The median mSWAT at last patient contact was 80 (0-400 IQR: 92). The median reduction in mSWAT for the whole population was 98 points, as presented in Table 5. The Wilcoxon sum test for paired data shows that this difference was statistically significant (p value= 0.0075). mSWAT changes discriminated by treatment response rates are shown in Figure 5.

The median VASP (pruritus assessment scale) before ECP treatment was 10 (0-10 IQR: 2). The median VASP at last patient contact was 6 (0-10 IQR: 96). The median reduction in VASP for the whole population was 4 points on the analogous visual scale, as shown in Table 6. The Wilcoxon sum test for paired data shows that this difference was statistically significant (p value= 0.0037). VASP changes discriminated by treatment response rates are shown in Figure 6.

Following ECP therapy, the overall response rate (ORR) was obtained in sixteen patients (64,7%), with a partial response (PR) in nine patients (52,9%), and complete response (CR) in two patients (11.8%). Only one patient (5.9%) had progression. All patients who obtained a complete response received combined

treatment. Of the nine patients who obtained a partial response, six received combined treatment. Of the five patients with stable disease, only one received combined treatment. The patient who had disease progression did not receive combined treatment. The response categories with combined treatment are shown in Figure 7.

At the time this study was closed, eight patients (47.6%) were still ongoing therapy, and five deaths (29.4%) were reported. Death causes were: sepsis in two patients, neuro infection in one patient, COVID-19 in one patient, and unknown cause of death in one patient.
Median survival for the entire group measured from the onset of treatment until death was not reached (95% CI: 859-NA). The 12-month survival probability was 82% (95% CI: 66-100%). The data is shown in Figure 8.

Discussion

Mycosis Fungoides (MF) and Sézary Syndrome (SS) account for the majority of cutaneous T-cell lymphomas (CTCL). These are rare entities and have variable clinical presentations [17]. Treatment options for advanced-stage MF and SS are limited, generally unsatisfactory, with low response rates and high toxicity for the patient [14].
The therapeutic strategies for CTCL adopted in the different cancer centers around the world are influenced by consensus, institutional preference, and the availability of treatment modalities. There is no available data on the impact that this variability of treatments may have on survival [7].
In 2017, Quaglino et. al published a multicenter retrospective study that included 853 patients from 21 specialized centers (14 European, 4 American, 1 Australian, 1 Brazilian, and 1 Japanese). This study showed that there is a great heterogeneity of treatment in mycosis fungoides in advanced stages and Sézary Syndrome in different institutions worldwide. The data found in this study revealed that chemotherapy as the first line of treatment is associated with an increased risk of death. Moreover, extracorporeal photopheresis is the most frequently used therapy as first-line treatment in SS or erythrodermic MF (stage III and IVA1) [18].
The mechanism of action of ECP in cutaneous T-cell lymphomas is not established. Theories supporting the therapeutic effect propose the induction of an immune response to the malignant T-cell clone. Although less than 10% of the total leukocyte population is treated during one procedure, the reduction in malignant T cells is usually greater than this percentage in peripheral blood [6]. This involves the following events: (1) induction of malignant T cell apoptosis, (2) conversion of circulating monocytes to immature dendritic cells, (3) presentation of dendritic cells (exposed to tumor cells) to cytotoxic T cells. and (4) expansion of a cytotoxic T cell population against the malignant T cell clone [19].
The results observed in this case series are comparable with those published to date. In our study, men were more commonly affected than women, as reported in other studies (incidence rate ratio [IRR] = 1.6) [8, 20]. The median age of our

study sample was 49 years (32-72 IQR 22), being 60.5 years in males and 43 years in females. Incidence rates reported for MF are similar among males and females at ages younger than 40 years, but notably higher among males at older ages [8].

Based on different consensus recommendations worldwide [9, 21, 22], most patients treated with ECP in our study were erythrodermic MF (stage III, T4N0-2M0B0-1) and SS (stage IVA1 or 2, T4N0-3M0B2). Although current guidelines for non-Hodgkin lymphoma do not recommend ECP as primary treatment in early-stage MF (IA, IB, IIA), in patients with the treatment-refractory disease, ECP is listed as a systemic treatment option[23].

Differences in the number of circulating Sézary cells per stage were identified. These differences were found to be significant between stage IVB and IB patients. This would be supported by current NCCN guidelines for Primary Cutaneous Lymphomas, which do recommend ECP as one of the primary treatments for SS and erythrodermic MF with B1 blood-stage but not for patients with erythrodermic MF with no evidence of blood involvement. Also, ECP is recommended in patients with stage IA, IB, and IIA disease and B1 blood involvement or those with the treatment-refractory disease [23], as mentioned above.

Although the identification of clonal TCR gene rearrangement has no prognostic value, it was helpful to determine clinical staging and assess relapsed or residual disease in some patients.

There is no evidence to suggest that topical therapies have a significant impact on the course of the disease for the advanced stages of MF/SS, although skin directed therapies can alleviate skin symptoms such as pain and pruritus, and most patients will require intermittent topical treatments, especially topical steroids [24]. Most of our patients (94.11%) received skin directed therapies previous to ECP. Phototherapy in the early stages of MF produces high complete remission rates, 70.58% of our patients had received the previous PUVA, and 5.88% UVB. However, patients with erythrodermic MF/SS are often intolerant of phototherapy due to aggravation of pruritus [24].

Response to systemic treatment of erythrodermic MF and SS is deficient. As there are currently no effective systemic therapies with long-lasting responses. The most widely described include i*nterferon alfa* with a dose-dependent response and in combination with systemic retinoids or methotrexate [25, 26]. In our study, all patients received systemic therapy. The average number of systemic lines before the start of ECP was 2.47 (SD: 1.17). The most frequent systemic therapies were *interferon*, *methotrexate*, and CHOP chemotherapy. The results of the treatment with systemic chemotherapy are unsatisfactory, with low response rates and high toxicity [14, 15]. It is usually a therapy that is reserved for patients with refractory disease, with a more palliative rather than curative use.

In their original publication, Edelson et al. Reported a response rate of 72.9% [1]. Since then, several case series and retrospective studies have been published confirming the efficacy of photopheresis, especially in patients with erythrodermic MF and SS, showing an ORR (overall response rate) around 60-63% and a

complete response rate around 20% [16, 27]. Results in our study are similar to those reported, with an ORR of 64,7%, partial response (PR) of 52,9%, and complete response (CR) of 11.8%. All patients who obtained a complete response received combined treatment and most of the patients who obtained a partial response received combined treatment. There is evidence to support higher response rates when ECP is combined with adjunctive therapies. Duvic et al, reported response rates of 40% in ECP monotherapy vs. 57% in combination of ECP plus IFN alfa, *bexarotene*, or GM- CSF in a group of patients with stage III/IV MF/SS [28]. In a retrospective review of 98 patients with SS treated with ECP combined with systemic IFN gamma, IFN alfa, GM-CSF, systemic retinoids, response rates of 75% were reported with a CR of 30% [29]. In a review of 34 patients with SS treated with ECP, IFN, and *bexarotene*, 88.2% of patients responded to the combined therapy, with a CR in 32.4% of patients [30]. The combination of ECP, IFN alfa/gamma, and *bexarotene* may lead to the highest response rates in patients with SS.

The reduction in the median of the mSWAT for the entire population was 98 points, being up to 400 points for the patients with complete response, with a median number of sessions performed per patient of 38. Edelson reported an average reduction of 64% of skin involvement after 22 weeks of treatment. These findings confirm the need for treatment as recommended by a minimum of 6 months [19].

The greatest impact on the quality of life of patients with MF / SS is pruritus, with limited options in pharmacological treatment that leads to a faulty response. All patients in our study presented a decrease in pruritus, with a median reduction in the visual analog scale (VASP) of 4 points.

In this study, median survival was not reached. The 12-month survival probability was 82% (95% CI: 66-100%). A follow-up analysis of the Edelson cohort published in 1992 showed a median survival of 60 months for patients who received ECP [31]. Similar median survivals were reported in other cohorts [32, 33]. The survival of patients with erythrodermic MF/SS on ECP remains to be confirmed with a prospective study.

ECP is usually well tolerated. Adverse effects reported are mostly related to discomfort and mild hematomas at venipuncture sites. Transient grade I hypotension (12%), grade I-II anemia (6%), hypokalemia (4%), and 1 urticarial eruption interpreted as a drug reaction to either 8- MOP or heparin were reported in a series of 51 patients [34]. In our study, adverse effects occurred in 2% of the performed sessions, of which, the most frequent complication was related to difficulties in venous access. The Deaths reported were not related to the treatment.

The mean treatment volume was 161 ml (SD: 32), lower compared to reported in a single and dual-needle configuration [35]. The reduction in total treatment time from 2.18 to 1.47 hours that was observed when comparing peripheral and central venous access raises the need for appropriate implantable devices to improve treatment times and optimize the use of the device.

Conclusion:

ECP should be considered as first-line therapy for erythrodermic MF/SS based not only on its efficiency and excellent side effect profile but also on the significant improvement of the symptoms, particularly pruritus. The addition of adjunctive immunostimulatory agents may increase the response to ECP. Peripheral or central venous access procedure is feasible and with currently available closed systems, the risk of complications is very low. Further studies are required to clarify the mechanism of action of ECP to better optimize therapy.

Declarations

Ethics approval: This study has been designed in coherence with the ethical guidelines and principles for research in human beings. Explicitly, the demands of international documents such as the Declaration of Helsinki and the Belmont Report, where fully embraced throughout the study. National documents such as resolution 8430 of 1993 where also used as a guideline. **This study is considered** a risk-free research, and has been approved by the IRB - Instutitional Review Board. Ethics comitee name: *Comité de Ética en Investigaciones del Instituto Nacional de Cancerología.* Reference Number: IX-0234533

Consent to participate: Verbal Informed consent was obtained from all individual participants included in the study. Approved by the ethics committee.

Consent for publication: Authors are responsible for correctness of the statements provided in the manuscript.

Availability of data and material (data transparency): Attached

Code availability (software application or custom code): Attached

Competing interests: The authors declare that they have no competing interests.

Funding: This study was supported by the *Instituto Nacional de Cancerología* in Bogotá, Colombia

Authors' contributions: All authors contributed, read and approved the final manuscript.

Acknowledgements: Not applicable

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Tables and Figures

Table 1: Distribution of diagnosis by sex

	Foliculotropic MF		Hyperpigmented MF		Sézary Syndrome		Total	
	n	%	n	%	n	%	n	%
Female	3	(42.9%)	1	(14.3%)	3	(42.9%)	7	(100.0%)
Male	3	(30.0%)	1	(10.0%)	6	(60.0%)	10	(100.0%)
Total	6	(35.3%)	2	(11.8%)	9	(52.9%)	17	(100.0%)

Table 2. Other population characteristics

	Foliculotropic MF	**Hyperpigmented MF**	**Sézary Syndrome**
n	6	2	9
Male (%)	3 (50%)	1 (50%)	6 (66.7%)
Contributive health system (%)	4 (66.7%)	2 (100%)	7 (77.8%)
Education (%)			
Elementary School	1 (16.7%)	2 (100%)	1 (11%)
Middle School	0	0	1 (11%)
High School	2 (33.3%)	0	0
Technician	0	0	2 (22.2%)
University Degree	1(16.7%)	0	3 (33.3%)
Master Degree	0	0	1 (11.1%)
No data	2 (33.3%)	0	1 (11.1%)
Origin (%)			
Urban	4 (66.7%)	1 (50%)	8 (88.9%)
Rural	2(33.3%)	1 (50%)	1 (11.1%)

Table 3. T-cell receptor (TCR) gene rearrangements detected in skin and blood samples

		TCR gene rearrangements detected in blood			
		Negative	Positive	No data	Total
TCR in Skin	Negative	1(33%)	0	2 (66.7%)	3
	Positive	0	3 (50%)	3 (50%)	6
	No data	0	1(12.5%)	7 (87.5%)	8
	Total	1	4(23.5%)	12 (70.6%)	17 (100%)

Table 4. ECP Treatment Characteristics discriminated by patient. Data of each variable are expressed as mean.

Patient Number	Number of Sessions	Duration (hours)	Treatment Volume (ml)	Psoralen Volume (ml)	Photoactivation Time (min)
1	10	2.18	157.00	2.56	23.90
2	7	2.30	145.00	2.40	24.00
3	38	2.29	149.00	2.48	24.30
4	51	2.22	150.00	2.50	24.20
5	6	2.23	151.00	2.52	24.80
6	32	2.02	173.00	2.89	25.00
7	57	2.22	164.00	2.71	22.60
8	66	2.18	156.00	2.60	25.70
9	70	2.07	160.00	2.66	30.00
10	44	2.21	186.00	3.12	25.80
11	77	2.23	157.00	2.63	31.30
12	77	2.05	199.00	3.33	27.60
13	44	1.98	156.00	2.62	21.40
14	14	2.23	181.00	3.07	28.40
15	13	1.34	220.00	3.68	33.80
16	2	2.09	173.00	2.90	21.50
17	8	1.64	189.00	3.25	29.20

Table 5. Median reduction in mSWAT of the entire population after ECP treatment.

	Median	Range	IQR
mSWAT Before ECP	178	70-400	100
mSWAT Last ECP	80	0-400	92
Difference	98		

Table 6. Median Reduction in VASP of the entire population after ECP treatment.

	Median	Range	IQR
VASP Before ECP	10	0-10	2
VASP Last ECP	6	0-10	96
Difference	4		

Figure 1. **a)** Stage at presentation **b)** TNMB staging categories

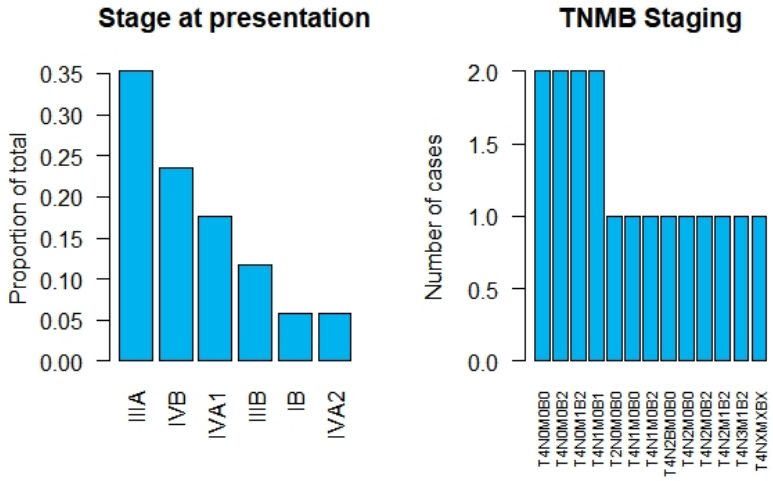

Figure 2. a) Differences in mean levels of Sézary´s Cells by Staging**. b)** Sézary´s Cells by Stage

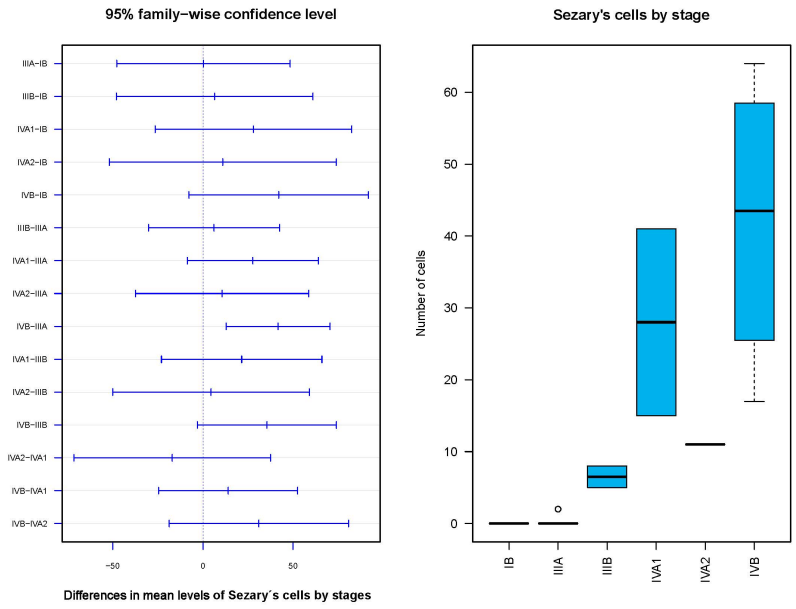

Figure 3. Systemic therapies received prior to the initiation of ECP. Other: chlorambucil, prednisolone, gemcitabine, brentuximab.

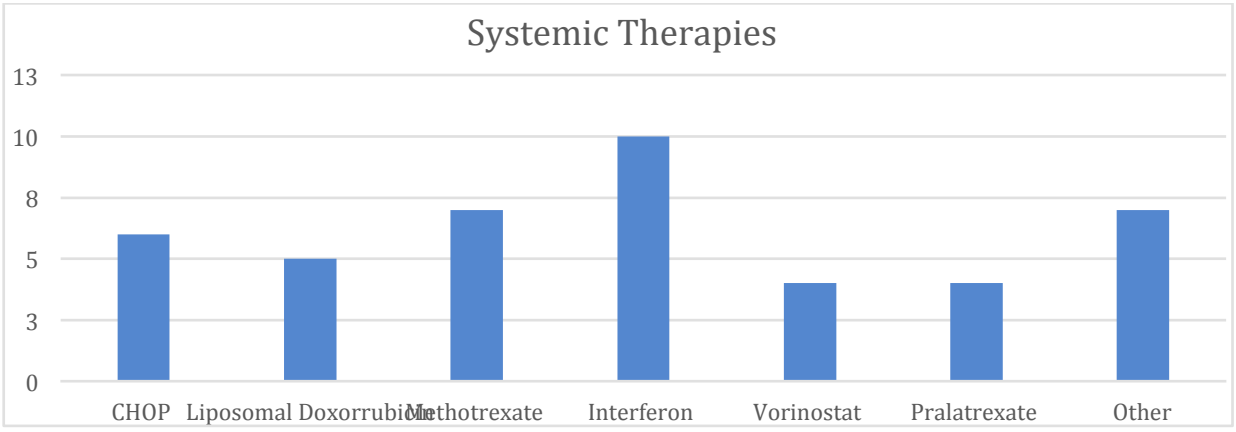

Figure 4. Number of ECP sessions received per patient. Green numbers represent active patients in treatment. Red numbers represent patients who discontinued treatment.

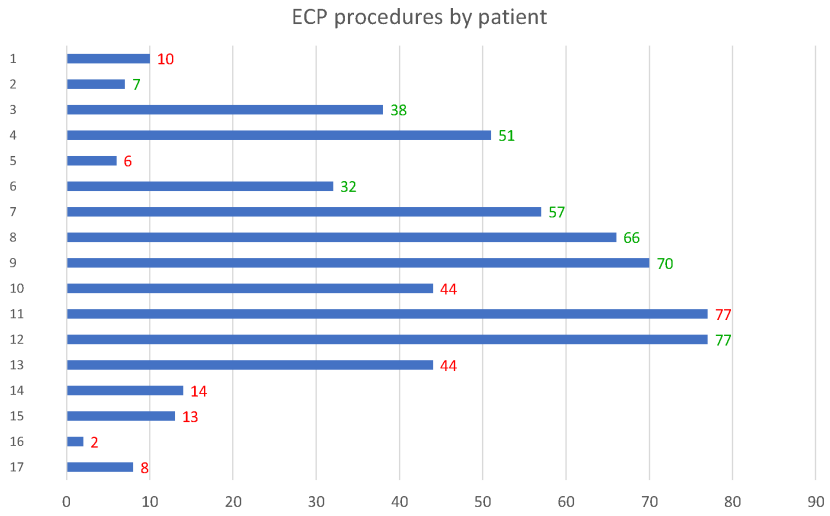

Figure 5. mSWAT changes discriminated by treatment response rates. CR: complete response, PR: partial respone, SD: stable disease, PD: progression disease.

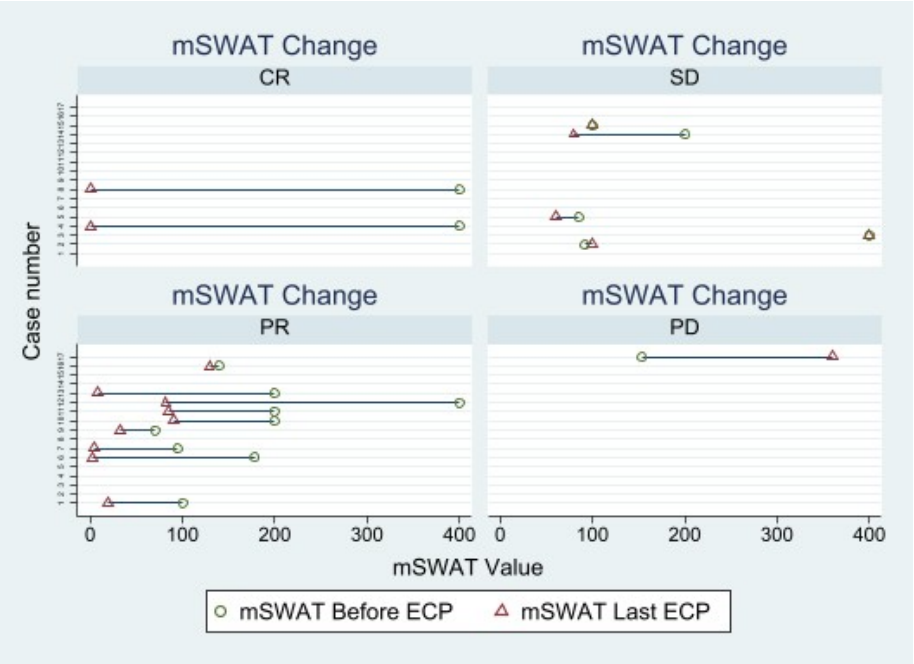

Figure 6. VASP changes discriminated by treatment response rates. CR: complete response, PR: partial respone, SD: stable disease, PD: progression disease

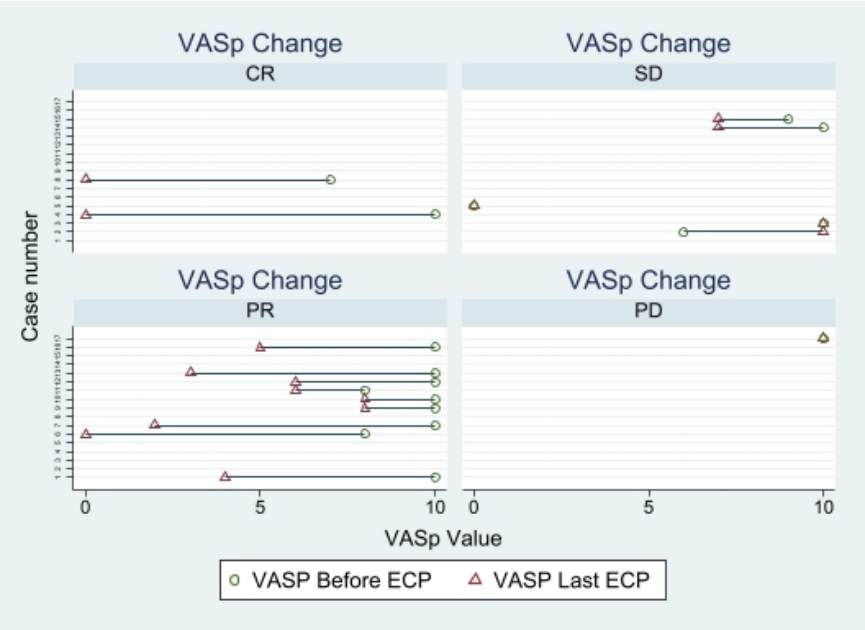

Figure 7. Response categories with combined treatment

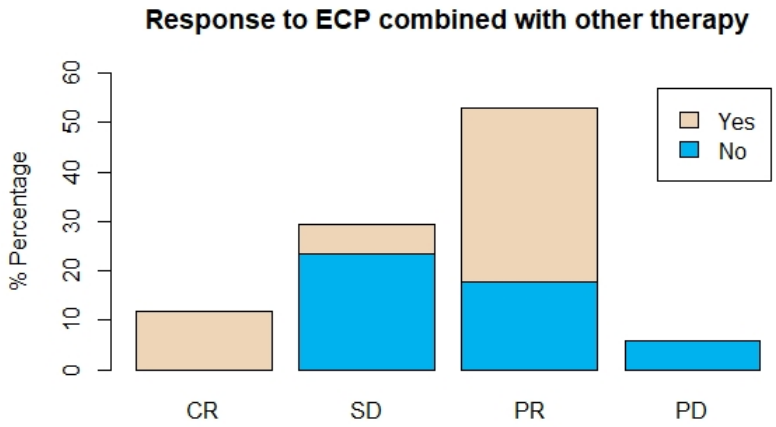

Figure 8. Overall survival