Hindawi
Dermatologic Therapy
Volume 2023, Article ID 9652322, 5 pages
https://doi.org/10.1155/2023/9652322

Research Article

Evaluating Photopheresis Regimens for Advanced CTCL: The Role of the SARS-CoV-2 Pandemic—A Single-Center Retrospective Study

Jori Hardin,[1] **Leah Cohen**,[2] **Alain Rook**,[3] **and Ellen Kim**[3]

[1]*University of Calgary, Division of Dermatology, Department of Medicine, Calgary, Canada*
[2]*Department of Dermatology, Hospital of the University of Pennsylvania, Philadelphia, USA*
[3]*Hospital of the University of Pennsylvania, Philadelphia, USA*

Correspondence should be addressed to Jori Hardin; jori.hardin@albertahealthservices.ca

Received 13 October 2022; Revised 13 January 2023; Accepted 21 March 2023; Published 31 March 2023

Academic Editor: Giuseppe Micali

Extracorporeal photopheresis (ECP) is an established, safe, and effective treatment for cutaneous T-cell lymphoma (CTCL). There is no published literature reviewing the clinical efficacy of ECP at varying frequencies or the ideal duration of therapy. The SARS-CoV-2 pandemic necessitated a reduced frequency of ECP for patients with CTCL at our center. We performed a retrospective chart review of patients with CTCL receiving ECP at the Penn Dermatology Photopheresis Service (PDPS) on March 1, 2020, and followed up their course until January 31, 2021. Our retrospective cohort study suggests that one day of ECP with extending duration between treatments can be considered an alternative maintenance regimen in appropriate patients with stable disease on concomitant multimodality immunomodulatory therapy.

1. Introduction

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of rare lymphoproliferative disorders. Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, with malignant lymphocytes residing in the skin. Sezary syndrome (SS) is considered a leukemic variant of cutaneous T-cell lymphoma, and diagnosis requires demonstration of a circulating malignant clone in the skin and blood [1]. The median overall survival in patients with stage IVA1 disease is 3.8 years [2].

Extracorporeal photopheresis (ECP) is an established, safe, and effective leukapheresis-based therapy for advanced CTCL. The original study of ECP in patients with treatment-resistant CTCL reported a response in 27 of 37 patients, with 9 having a complete response [3]. A complete response was seen in 30% of patients ($n = 29$), and a significant clinical improvement was achieved in 75% of patients with multimodality therapy in our case series of CTCL patients treated with ECP and 1 or more systemic immunomodulatory agents for at least three months [4]. ECP is well tolerated with no reports of grade III/IV adverse effects following treatment [5]. ECP is now mostly performed in the outpatient setting, and treatment duration ranges from 1.5 to three hours. The THERAKOS CELLEX photopheresis system is only available at selected institutions, and the protocol requires highly skilled staff, thereby making it often inaccessible geographically and demanding of time.

Remarkably, current treatment intervals remain identical today to regimens published by Dr. Edelson in 1987 [3]. There is no published literature reviewing the clinical efficacy of ECP at varying frequencies or the ideal duration of therapy. Furthermore, there are no data published, to our knowledge, regarding frequency of disease flare/progression on ECP monotherapy at the standard regimen. Current consensus guidelines recommend one cycle on two consecutive days every 2–4 weeks with the option for more frequent cycles in symptomatic patients and those with a high tumor burden [5]. Tapering of ECP is also highly ambiguous. An update from the UK Photopheresis Society

Table 1: Patients with CTCL receiving ECP at PDPS on March 1, 2020, until January 31, 2021, comparing pre- and post-pandemic ECP regimens.

Sex	Age	Race	Diagnosis	Stage at diagnosis	Stage before pandemic	Months on ECP before 3/2022	B stage before pandemic	Other treatments on before pandemic	ECP frequency before pandemic	ECP frequency after pandemic	First treatment back documented flare?	Changes in therapy due to flare or progression within 6 months after frequency change	Changes in therapy
M	77	W	SS	IVA1, T4N0M0B2	IVA1, T2N0M0B2	107	B2	Intron A, isotretinoin, TS	2d q4w	1q4w	N	N	None
M	66	W	MF	IIIB, T4NXMXB1	IIIB, T4NXMXB0	14	B0	Intron A, Targretin	2d q4w	1q4w	N	N	None
M	44	W	MF	IB, T2N0M0B1	IB, T2N0M0B1	19	B1	Intron A, TS, methotrexate	2d q5w	1q4w	N	N	None
M	69	W	SS (FMF, LCT)	IVA1, T4NXM0B2	IA, T1N0M0B0	93	B0	Sylatron, Targretin, TS	2d q6w	1q4w	N	N	None
M	61	W	MF	IIIB, T4N0M0B1	T0N0M0B0	28	B0	Targretin, TS	2d q5w	1q4w	N	N	None
M	68	B	MF	IIIB, T4NXM0B1	T0N0M0B0	61	B0	Actimmune, Dupixent	2d q7w	1q8w	N	N	None
F	75	W	MF	IIIB, T4NXM0B1	IA, T1N0M0B0	31	B0	Targretin, Actimmune	2d q6w	1q4w	N	N	None
M	57	B	MF	IIIA, T4NXM0B0	IB, T2N0M0B0	28	B0	Actimmune, methotrexate, TS	2d q3w	1q3w	Y, increased pruritus with stable BSA	Y (Fl)	Increased methotrexate dose due to itch
F	73	W	MF	IIIA, T4NXMXB1	IB, T2NXMXB1	12	B1	Targretin, Intron A, carmustine, TS	2d q4w	1q4w	N	Y (Fl)	Started phototherapy due to increased BSA
F	78	W	SS	IVB, T4NXM1B2	IVB, T4NXM1B2	15	B2	Actimmune, TS	2d q4w	1q4w	N	N	Started Moga due to stable B2 involvement
M	82	W	SS	IVA1, T4N0M0B2	T0NXM0B0	98	B0b	Actimmune, Targretin	2d q5w	1q5w	N	N	None
F	66	W	SS	IVA1, T4NXM0B2	T0N0M0B0	204	B0	Intron A	2d q5w	1q5w	N	N	None
M	75	B	MF	IIIA, T4N0M0B0	T0N0M0B0	12	B0	Actimmune, Targretin, TS	2d q4w	1q4w	N	N	None
M	78	W	MF	IIIA, T4N0M0B0	IA, T1N0M0B0	65	B0	Targretin, Actimmune, TS	2d q4w	1q4w	N	N	None
M	56	B	MF (FMF)	IA/IB, T1/2NXM0B1	IB, T2N0M0B1	45	B0	Actimmune, isotretinoin, TS	2d q4w	1q5w	N	N	None
M	64	W	MF	IIIB, T4NXM0B0	IA, T1N0M0B0	182	B0	Actimmune, Sylatron, Targretin, isotretinoin	2d q5w	1q5w	N	N	None
F	56	B	MF	IIIB, T4NXM0B1	IB, T2NXM0B0	50	B0	Targretin, Actimmune, TS	2d q6w	1q6w	N	N	None
M	52	B	SS (FMF)	IVA1, T4N1-2M0B2	T0NXM0B0	31	B0	Targretin, Actimmune, TS	2d q4w	1q4w	Y, erythrodermic with palpable LN	Y (PD)	Came off home maintenance regimen due to loss of insurance and became erythrodermic, got TSEBT
M	66	W	MF	IIIA, T4N0M0B0	IB, T2N0M0B0	51	B0	Targretin, Actimmune, TS	2d q7w	1q7w	N	N	None

Table 1: Continued.

Sex	Age	Race	Diagnosis	Stage at diagnosis	Stage before pandemic	Months on ECP before 3/2022	B stage before pandemic	Other treatments on before pandemic	ECP frequency before pandemic	ECP frequency after pandemic	First treatment back documented flare?	Changes in therapy due to flare or progression within 6 months after frequency change	Changes in therapy
M	69	W	SS	IVA1, T4NXM0B2	IVA1, T4NXM0B2	10	B2	Actimmune, TSEBT, TS	2d q3w	1q4w	N	N	None
M	89	B	SS	IVA1, T4N0M0B2	T0-2N0M0B1	107	B1	Targretin, Actimmune, TS	2d q6w	1q6w	N	N	None
F	65	W	MF	IIIB, T4NXM0B1	T1NXM0B0	35	B0	Targretin, Intron A, TS, carmustine	2d q4w	1q5w	N	N	None
F	81	B	MF	IB, T2N0M0B1	IA, T1N0M0B0	85	B0	Targretin, Intron A, Valchlor, TS	2d q8w	1q8w	N	N	None
M	82	W	MF	IVA2, T2N3M0B1	T0NXM0B0	58	B0	Intron A, Targretin	2d q8w	1q8w	N	N	None
F	74	B	MF (LCT)	IVA1, T1N0M0B2	T0N0M0B0	87	B0	Targretin, Intron A, imiquimod, TS	2d q4w	1q4w	N	N	None
F	57	B	SS (LCT)	IVA2, T4N3M0B2	IA, T1N0M0B0	92	B0	Targretin, carmustine, TS	2d q6w	1q4w	N	N	None
F	65	W	SS	IVA1, T4N1M0B2	IIA, T2N1M0B0	5	B0	Actimmune, Intron A, TS	2d q4w	2d q4w	Y, slightly increased pruritus and BSA	Y (Fl)	Started Targretin
F	61	W	SS	IVA2, T4N3M0B2	IVA2, T4N3M0B2	11	B2	Targretin, Intron A, Actimmune, TS	2d q4w	2d q4w	N	N	Started Moga due to stable B2 involvement
F	75	W	SS	IVA1, T4N0M0B2	IVA1, T2N0M0B2	4	B2	Intron A, carmustine, TS	2d q4w	2d q4w	Y, increased pruritus and BSA	Y (Fl)	Got TSEBT, started Actimmune and mogamulizumab due to stable T2 skin and stable B2 involvement
M	54	W	MF (FMF)	IIIB, T4N1M0B1	T1N1M0B0	29	B0	Isotretinoin, PUVA, TS	2d q4w	2d q4w	N	Y (PD)	Initiated Dupixent March 2020, erythrodermic July 2020, off Dupixent, started Moga 7/2020
M	71	W	MF	IIIB, T4N1M0B1	IIA, T2N1M0B1	16	B0	Actimmune, Targretin, TS	2d q4w	1d q2w	N	Y (PD)	Off all treatment during hospitalization 6/2020 and became erythrodermic

F: female, M: male, W: white, B: black, SS: Sezary syndrome, MF: mycosis fungoides, FMF: folliculotropic mycosis fungoides, LCT: large cell transformation, TS: topical steroids, PUVA: psoralen UVA, BSA: body surface area, LN: lymph nodes, Y: yes, N: no, Fl: flare, PD: progressive disease, Moga: mogamulizumab, and TSEBT: total skin electron beam therapy.

proposes indefinitely continuing ECP treatment in patients with complete, partial, or minimal clinical response due to its safety profile, synergy with other immunomodulatory medications, and a paucity of other efficacious treatment options for advanced disease [6]. With our current understanding of the immunologic mechanism of ECP, the optimal frequency of therapy remains unclear.

The standard starting regimen at the Penn Dermatology Photopheresis Service (PDPS) is 2 consecutive days every four weeks. Treatment with ECP is most often layered with other immunomodulatory modalities [4]. Typically, once a patient has achieved a durable response, tapering ECP begins by decreasing the frequency by one week between cycles, while continuing two consecutive treatment days for each cycle, at a frequency of every 12 weeks.

At the onset of the SARS-CoV-2 pandemic, due to the uncertainty regarding the risk of transmission and mortality of COVID-19, ECP treatments were temporarily halted for 8 weeks (March 15–May 13, 2020) and then resumed with reduced patient volume to create COVID-safe pathways in concordance with national recommendations (issued prior to the development of effective COVID-19-specific therapies and vaccines) [7]. Clinically stable patients were decreased from two consecutive days of ECP per cycle to one day only.

2. Methods

We performed a retrospective chart review of patients with CTCL receiving ECP at the PDPS on March 1, 2020, and followed up their course until January 31, 2021 (Table 1). All patients on multimodality immunotherapy with ECP as a pillar of their treatment were included in the study. Patients were followed up for eight months after ECP was restarted following the first wave of the pandemic, and outcomes were recorded. Progression of disease was defined based on accepted clinical endpoints and response criteria [8, 9]. We defined a flare of disease as any worsening of the disease that did not meet the criteria for progression, including a change in symptoms such as pruritus.

3. Results

Our patient cohort ($n = 31$) consisted of 12 women and 19 men, 10 Black and 21 White, with an average age of 67.8 years. There were 12 patients with SS and 19 with MF. Histologically, three patients had large cell transformation, and four had folliculotropism. All patients were on multimodality immunomodulatory therapy, which included interferon, retinoids, and skin-directed therapy. There were two patients on methotrexate and one on dupilumab. The median number of months on ECP prior to March 1, 2020, was 35. Twenty-six out of 31 patients decreased the frequency of ECP after pausing during the first wave of the pandemic from 2 consecutive days per treatment cycle to one day per cycle to mitigate the risks of COVID-19 in concordance with national cutaneous lymphoma pandemic guidelines [7]. All of these patients had stable disease and demonstrated a durable response to treatment prior to making this shift.

At the first assessment following the two-month hiatus from ECP, one patient had a subjective flare with increased pruritus but had stable examination and blood staging, and one patient had progressive disease with erythroderma and lymphadenopathy (remaining B0). Notably, this patient also had an interruption of their systemic regimen. Eight months after each patient resumed ECP (at the reduced one day per cycle frequency), one additional patient had a disease flare with increased body surface area involvement prompting initiation of phototherapy. None of the patients went off ECP multimodality therapy.

4. Discussion/Conclusion

In CTCL, there is an accumulating body of evidence to show that there is a complex interplay between the host immune system and the immune response incited by 8-methoxypsoralen and UVA-treated cells. Interestingly, in patients with Sezary syndrome, who have demonstrated a complete response in blood, consensus guidelines generally recommend continuing ECP treatment [6]. The exact immunomodulatory effects of ECP have yet to be uncovered. There have been no randomized controlled trials validating ECP compared to conventional treatment modalities for CTCL or has the optimal frequency of ECP, and the necessity for two consecutive treatment days per cycle has been studied in controlled trials. In the original literature, the duration of ECP was decided by technology as the rate of infusion was such that, to receive the therapeutic regimen, patients needed two consecutive days [3]. The COVID-19 pandemic initially necessitated reduced ECP regimens at our center in order to ensure the health and safety of patients and staff, and our decision to reduce ECP frequency was informed by national guidelines [7]. We determined that all patients with CTCL receiving ECP as part of multimodality therapy, who were clinically and biochemically stable, would decrease the frequency of ECP to one day per cycle primarily to mitigate the risks of COVID-19. Twenty-five of the twenty-six patients with the reduced ECP frequency did not develop disease flare or progression up to 8 months following the change in regimens. Our retrospective cohort study suggests that one day of ECP with extending duration between treatments can be considered an alternative maintenance regimen in appropriate patients with stable disease on concomitant multimodality immunomodulatory therapy. However, this conclusion should be further studied in multicenter prospective controlled trials evaluating optimal ECP regimens. It is our hope that, with reduced intensity regimens, ECP might become more accessible to patients who live outside ECP center catchment areas and further create availability for a scarce and demanding resource at a given institution.

Data Availability

The clinical data used to support the findings of this study are included within the article.

Conflicts of Interest

Dr. A Rook works at TLR Biosciences Consultant, Soligenix Advisory Board.

References

[1] R. Willemze, L. Cerroni, W. Kempf et al., "The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas," *Blood*, vol. 133, no. 16, pp. 1703–1714, 2019.

[2] R. A. Wilcox, "Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk-stratification, and management," *American Journal of Hematology*, vol. 92, no. 10, pp. 1085–1102, 2017.

[3] R. Edelson, C. Berger, F. Gasparro et al., "Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy," *New England Journal of Medicine*, vol. 316, no. 6, pp. 297–303, 1987.

[4] B. A. Raphael, D. B. Shin, and K. R. Suchin, "High clinical response rate of sezary syndrome to immunomodulatory therapies: prognostic markers of response," *Archives of Dermatology*, vol. 147, no. 12, pp. 1410–1415, 2011.

[5] R. Knobler, P. Arenberger, A. Arun et al., "European dermatology forum – updated guidelines on the use of extracorporeal photopheresis 2020 – part 1," *Journal of the European Academy of Dermatology and Venereology*, vol. 34, no. 12, pp. 2693–2716, 2020.

[6] A. Alfred, P. C. Taylor, F. Dignan et al., "The role of extracorporeal photopheresis in the management of cutaneous T cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society," *British Journal of Haematology*, vol. 177, no. 2, pp. 287–310, 2017.

[7] J. A. Zic, W. Ai, O. E. Akilov et al., "United States Cutaneous Lymphoma Consortium recommendations for treatment of cutaneous lymphomas during the COVID-19 pandemic," *Journal of the American Academy of Dermatology*, vol. 83, no. 2, pp. 703-704, 2020.

[8] J. J. Scarisbrick, E. Hodak, M. Bagot et al., "Blood classification and blood response criteria in mycosis fungoides and sezary syndrome using flow cytometry: recommendations from the EORTC cutaneous lymphoma task force," *European Journal of Cancer*, vol. 93, pp. 47–56, 2018.

[9] E. A. Olsen, S. Whittaker, Y. H. Kim et al., "Clinical end points and response criteria in mycosis fungoides and sézary syndrome: a consensus statement of the international society for cutaneous lymphomas, the United States cutaneous lymphoma consortium, and the cutaneous lymphoma task force of the European organisation for research and treatment of cancer," *Journal of Clinical Oncology*, vol. 29, no. 18, pp. 2598–2607, 2011.