Outcome of extracorporeal photopheresis in mycosis fungoides patients is not predicted by quotients of systemic immune-inflammatory biomarkers

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Abstract
Background: Systemic immune-inflammatory biomarkers (SIIBs) have not been studied in mycosis fungoides (MF) patients undergoing extracorporeal photopheresis (ECP).

Objective: The objective was to determine whether recently proposed SIIBs are suitable to predict ECP treatment outcome and overall prognosis of patients with MF.

Methods: Twenty-nine MF patients were retrospectively evaluated who had undergone ECP. SIIBs included neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and pan-immune-inflammation value.

Results: Lymphocyte count ($P = .021$), CD4$^+$/CD8$^+$ cells ($P = .00006$), CD4$^+$/CD56$^+$ NK cells ($P = .00008$), and LDH levels ($P = .0041$) significantly declined after 6-month ECP. We could not detect significant cutoff values for baseline SIIBs capable of predicting advanced disease, overall response to 6-month ECP, or 5-year lymphoma-specific (LS) survival ($P > .05$). Circulating baseline counts of CD4$^+$/CD7$^-$ cells (cutoff: $\leq 12.2$; $P = .010$) and CD4$^+$/CD26$^-$ cells (cutoff: $\leq 19.5$; $P < .0001$) significantly predicted ECP treatment response after 6 months. Moreover, CD4$^+$/CD8$^+$ ratio (cutoff: $> 1.34$; $P = .045$) and increased thrombocyte counts (cutoff: $> 259,000$; $P = .010$) were baseline predictors for 5-year LS death.

Conclusion: ECP appears to be beneficial in early-stage CTCL as well. Lower percentages of circulating CD4$^+$/CD7$^-$ and CD4$^+$/CD26$^-$ lymphocytes at baseline correlate with response to ECP. In this study, however, baseline SIIBs did not appear to serve as suitable biomarkers for the prediction of treatment outcome and LS survival.

1 | INTRODUCTION

Extracorporeal photopheresis (ECP) is a well-tolerated technique of photochemotherapy, which has been proven to be effective in cutaneous T-cell lymphoma (CTCL), particularly in erythrodermic CTCL and Sézary syndrome (SS), when circulating tumor clones are increasingly present in the peripheral blood. However, improvements
have also been observed in patients with non-erythrodermic mycosis fungoides (MF) in the early stages, even when tumor cells cannot be detected in the peripheral blood.\textsuperscript{1-4}

Since there is a need for robust biomarkers predicting treatment response and overall prognosis of patients with lymphomas, a group of systemic immune-inflammatory biomarkers (SIIBs) have been proposed in the recent literature. Indeed, simple blood biomarkers, including neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR), have been suggested as prognostic baseline biomarkers in Hodgkin disease, B-cell lymphomas, natural killer cell lymphomas, and peripheral T-cell lymphomas.\textsuperscript{5-8} Cengiz and co-workers\textsuperscript{9} were the first research group reporting on the prognostic performance of the NLR in patients with MF. However, they did not assess NRL in the context of a given treatment setting. Here, we wished to determine whether recently proposed SIIBs are suitable to predict ECP treatment outcome and overall prognosis of patients with MF.\textsuperscript{5-11}

\section*{2 \quad \textbf{MATERIAL AND METHODS}}

\subsection*{2.1 \quad Patients}

For this retrospective analysis, we included patients with MF who were treated with ECP at the Department of Dermatology, Ruhr-University, Bochum, Germany. Only MF patients who had a history of at least 3 cycles of ECP treatment were included. We exclusively studied MF patients from their first ECP procedure on up to a maximum of 6-month treatment. Previous and concomitant therapies were also evaluated. MF outcomes after ECP (0 = progressive disease, 1 = stable disease, 2 = partial response, and 3 = complete response) were extracted from the electronic database records. Lymphoma-specific (LS) survival data were collected using chart review and by contacting patients, relatives, network data, general practitioners as well as specialists such as dermatologists and hematologists. A healthy gender- and age-matched group was recruited as controls for the baseline SIIBs investigated. The study was conducted according to the Declaration of Helsinki and followed a protocol approved by our institutional ethics review board (#16-5985).

\section*{3 \quad \textbf{ECP}}

ECP treatment was performed using UVAR XTS (Therakos Inc.,) or CELLEX (Mallinkrodt, Dublin, Ireland) instruments as recommended by updated European Dermatology Forum guidelines.\textsuperscript{4,5} Almost all patients started ECP via peripheral venous access. During the course of treatment, however, a port catheter (TITAN-PORT D, PakuMed GmbH) was implanted in three patients. ECP was performed on 2 consecutive days.
every 2 weeks over a 6- to 12-week period; following this period, ECP was conducted on 2 consecutive days on a monthly basis. Heparin was used as anticoagulant.

4 | BLOOD PARAMETERS

The following blood parameters were collected via cubital fossa venipuncture in the morning prior to ECP procedures at baseline (ECP naïve) and after 3- and 6-month of ECP: eosinophil, neutrophil, monocyte, lymphocyte and platelet counts, NLR, platelet-to-lymphocyte ratio (PLR), LMR, pan-immune-inflammation value (PIV) [neutrophils \((10^3/mm^3) \times \) platelets \((10^3/mm^3) \times \) monocytes \((10^3/mm^3)\)/ lymphocytes \((10^3/mm^3)\)], lactate dehydrogenase (LDH), CD4+/CD26- lymphocytes, CD4+/CD7- lymphocytes, CD4+/CD8+ ratio, CD3+/CD8+, and CD4+/CD56+ natural killer (NK) cells.\(^5\) Heparin was used as anticoagulant.

4.1 | Statistics

Data analysis was performed using the Statistical Package MedCalc Software version 19.6.1 (MedCalc, Ostend, Belgium). The distribution of data was assessed by the D’Agostino-Pearson test. The mean and SD were calculated for normally distributed data; the median and range were calculated for non-normally distributed data. Six-month laboratory data were analyzed using Friedman’s ANOVA. Moreover, we used the Spearman correlation procedure and chi²-square test. The optimal cutoff value for predictive variables was determined by using ROC.
curve analyses. 5-year LS survival (Kaplan–Meier curve) was calculated from the beginning of the first ECP cycle to the time of the event (LS death) or last follow-up. P-values less than .05 were considered statistically significant.

5 | RESULTS

As shown in Table 1, more than half of MF patients (n = 29) investigated had early-stage disease (15/29, 51.7%), and the remaining patients (14/29, 48.3%) were in stages IIb, IIIa and IIIb. Several blood parameters declined significantly during the 6-month period of ECP treatment (Table 2). These included lymphocyte count (P = .021), CD4+/CD8+ cells (P = .00006), and CD4+/CD56+ NK cells (P = .00008). Moreover, LDH levels significantly decreased during the 6-month ECP therapy period (P = .0041), whereas LMR significantly declined after 6 months (P = .019), and PLR significantly increased after 3- and 6-month ECP treatment (P = .038). Importantly, median baseline NLR, PRL, LMR, and PIV quotients of MF patients did not significantly differ from gender- and age-matched healthy controls (P > .05, Table 3). Using ROC analyses, we could not detect significant cutoff values for baseline SIIBs (NRL, PRL, LMR, and PIV) capable of predicting advanced disease, overall response to 6-month ECP, or 5-year LS survival (P > .05). 5-year LS survival is shown in Figure 1, whereas NRL, PRL, and PIV positively correlated with each other (r-values: .70 to .74; P < .0001), and LMR inversely correlated with NRL, PRL, and PIV (r-values: −.64 to −.74; P = .0002 to P < .0001). Circulating baseline counts of CD4+/CD7- cells (cutoff: ≤12.2; P = .010) and CD4+/CD26- cells (cutoff: ≤19.5; P < .0001) significantly predicted ECP treatment response after 6 months. Moreover, CD4+/CD8+ ratio (cutoff: >1.34; P = .045) and increased thrombocyte counts (cutoff: >259 000; P = .010) were baseline predictors for LS death.

6 | DISCUSSION

ECP is an immunomodulating photochemotherapeutic method that results in an expansion of peripheral blood
dendritic cell populations and an increased T helper cell 1 immune response in patients with CTCL. ECP is considered first-line therapy for erythrodermic MF and SS. Patients with a measurable, but rather low blood tumor burden, are most likely to respond to ECP, and the addition of adjunctive immunomodulatory agents may increase response rates. There may be a role for ECP in the treatment of refractory early-stage MF, but data are limited. In the present study, we have confirmed that response to ECP is associated with a measurable but low blood tumor burden. Indeed, we found that a lower percentage of CD4+/CD7- and CD4+/CD26- lymphocytes in the peripheral blood at baseline were associated with response to a 6-month treatment period of ECP. In contrast, a higher ratio of CD4+/CD8+ cells at baseline was associated with a higher risk of LS death. Stevens et al. also showed that a low number of CD4+/CD7- lymphocytes in the circulation correlated with response to ECP treatment after 5 months of therapy. Talpur et al. recently demonstrated that ECP is effective for patients with early-stage MF (stage Ia) with low toxicity and improved quality of life, either alone or in combination with biologic response modifiers. By contrast, Child et al. concluded from their data that ECP is not effective in the treatment of early-stage MF even in patients with molecular evidence for a T-cell clone in peripheral blood. Miracco et al. studied histological changes in early-stage MF under ECP therapy. They found that ECP appears to stimulate a CD4+/CD8+ cell-mediated anti-clonotypic activity against circulating pathogenic clones resulting in tumor cell death by apoptosis. Indeed, the decline of CD4+/CD8+ lymphocytes observed in the present study may be explained by an enhanced consumption of these cells during 6 months of ECP treatment. However, much to our surprise, we did not observe a significant decrease of circulating CD4+/CD7- and CD4+/CD26- cell clones. Nonetheless, the significant decrease of LDH levels observed in the present study indicates improvement of MF after a treatment period of 6 months.

The investigation of interactions between chronic inflammatory processes and malignancies continues to attract interest. Inflammatory processes have been demonstrated to promote tumor initiation and progression, while escape from immune surveillance results in tumor progression. Within the tumor microenvironment, neutrophil granulocytes, monocyte-derived macrophages, and thrombocytes can contribute to remodeling of the extracellular matrix, promote angiogenesis, and stimulate tumor growth directly and indirectly, thus contributing to disease progression. In contrast, the presence of tumor-infiltrating lymphocytes is associated with a more favorable outcome. Based on the hypothesis that peripheral blood cell counts and their ratio can provide information about the status of the tumor microenvironment, blood cell-derived SIIBs, including NLR, LMR, and PLR, were shown to have prognostic properties in many cancers. Last year, Fuca and co-workers reported for the first time that PIV could serve as a novel SIIB, performing better in predicting survival outcomes than other SIIBs in patients with advanced colorectal cancer patients. However, the predictive and/or prognostic performance of PIV has not been studied in patients with lymphoma. Unlike Choi and colleagues, who found that thrombocytopenia at primary diagnosis is an independent prognostic factor for worse survival in patients with peripheral T-cell lymphoma, we observed that increased thromocyte counts were associated with LS death. In line with our data, Rachidi et al. observed that thrombocytosis was associated with reduced overall survival of patients with melanoma. In the present study, however, we did not observe significant differences in baseline SIIBs (NRL, PRL, LMR, and PIV) in CTCL patients and gender- and age-matched healthy controls. Moreover, we did not detect a significant association between these SIIBs and clinical outcomes (disease stage, treatment response, and LS survival). In particular, NLR and PLR values have frequently been studied in a variety of malignancies and inflammatory conditions. For example, in melanoma patients with metastatic disease, higher NLR and PLR values are associated with worse prognosis. By contrast, low NLR and PLR values have been correlated with worse prognosis in melanoma patients in stages I–III. Moreover, SIIBs also appear to correlate with treatment response to immunotherapy and the occurrence of immune-related adverse events in melanoma patients. In patients with Merkel cell carcinoma, PIV appears to predict independently disease recurrence. By contrast, we have recently also shown that PIV seems not to be a significant predictor for clinical outcome measures of melanoma patients under immune checkpoint inhibitor therapy. With regard to CTCL, only one study exists that investigates prognostic factors such as NLR. Specifically, a mean baseline NLR of 2.07 ± 1.17 was observed in the patient group (n = 119), whereas the NLR was significantly lower in the control group (1.76 ± 0.53). Moreover, a baseline NLR of 2.85 or higher was positively correlated with advanced disease stage and disease progression. Of course, we cannot exclude the absence of a significant prognostic value for SIIBs investigated in our study due to the relatively small number of patients. Apart from the small sample size, this study had a number of other limitations, since retrospective studies are prone to selection bias, recall bias, or misclassification bias and are subject to confounding. However, the primary aim of the study was to assess changes in several blood parameters, which might be relevant for the resolution of MF and suitable as prognostic baseline biomarkers. Importantly, the changes in blood parameters and
clinical outcome observed in the present study cannot be ascribed to ECP alone but must be considered in the context of concomitant therapies employed.

Nonetheless, we conclude that ECP appears to be beneficial in early-stage CTCL as well. Moreover, lower percentages of circulating CD4+/CD7- and CD4+/CD26+ lymphocytes at baseline were correlated with response to ECP. Finally, in this study, baseline SIIBs did not appear to serve as suitable biomarkers for the prediction of treatment outcome and LD survival.

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CONFLICT OF INTEREST
T.G. has received speakers and/or advisory board honoraria from BMS, Sanofi-Genzyme, MSD, Novartis Pharma, Roche, AbbVie, Almirall, Janssen, Lilly, Pfizer, Pierre Fabre, and Merck Serono, outside the submitted work. L.S. has received speakers and/or advisory board honoraria from BMS, Sun Pharma, MSD, and Novartis. R.S. has received speakers and/or honoraria from Kyowa Kirin, Takeda, Novartis, and Recordati Rare Diseases. All other authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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