Received: 17 February 2020 | Revised: 6 May 2020 | Accepted: 9 June 2020

DOI: 10.1111/exd.14133

ORIGINAL RESEARCH ARTICLE

Experimental Dermatology WILEY

Systemic chemotherapy promotes HIF-1α-mediated glycolysis and IL-17F pathways in cutaneous T-cell lymphoma

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Funding information
This study was supported in part by research funding from the National Key Clinical Specialty (grant No. 2012649) to J.Z and National Natural Science Foundation of China (grant No. 30901293) to XS.

Abstract

Background: Systemic chemotherapy is often the last resort of advanced cutaneous T-cell lymphoma (CTCL). Tumor recurrence and adverse effects of systemic chemotherapy are the main limitations.

Objective: We aim to investigate the metabolic alterations in tumor cells after CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone) chemotherapy.

Methods and Results: In advanced CTCL, CHOP chemotherapy has no survival benefit and the duration of response is significantly inferior to other canonical treatments. HIF-1α is significantly elevated in lesions of advanced MF patients as well as tumor cell line Hut78 and tumor xenograft mice model. CHOP therapy also increased glycolytic activities in a HIF-1α-dependent manner. In CTCL xenograft tumor mice model, lesional cells showed a significant increase in IL-17F after chemotherapy, shifting toward a Th17 phenotype, which process is also regulated by HIF-1α. Echinomycin, HIF-1α inhibitor, was co-administered in xenograft tumor mouse models with CHOP and showed a significant reduction in tumor growth.

Conclusion: CHOP chemotherapy promotes glycolysis and IL-17 pathways in a HIF-1α-dependent fashion. Furthermore, HIF-1α blockade is promising as an accompanying agent in systemic chemotherapy for patients with advanced CTCL.

KEYWORDS
cancer, cutaneous T-cell lymphoma, HIF-1α, mycosis fungoides, pathogenesis, T cell

1 | INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is the most common primary cutaneous lymphoma, accounting for approximately 75% of all cutaneous lymphomas.[1-3] Various prognostic markers are important to estimate disease progression and guide therapeutics.[4,5] There are various treatment modalities available for mycosis fungoides (MF), the most common type of CTCL; skin-derived therapies and UV radiations are preferred for early-stage MF. Systemic therapies are often reserved for patients with advanced MF and other types of CTCL. These include systemic multi-agent chemotherapies, interferon-α, bexarotene, HDAC inhibitors, immunotoxins and allogeneic hematopoietic stem cell transplantation.

Hughes et al retrospectively analysed the effectiveness of systemic chemotherapy in 144 MF and SS cases; median time to next treatment (TTNT) was 3.9 months, which is the shortest compared with other systemic therapies.[6] It has been shown that systemic chemotherapies did not improve prognosis of patients

Bo Wang and Kejia Li have equal contribution to this manuscript.

with early-stage MF.[7,8] Systemic chemotherapy temporarily suppresses tumor growth; however, tumor recurs much faster compared to other treatment modalities. The molecular basis of limited efficacy of aggressive chemotherapy in advanced CTCL is still not clear.

It is hypothesized that chemotherapy either alters oncogenic potential of tumor cells or it tunes microenvironment more favourable toward tumor growth. Reprogramming of metabolism is critical for cancer cells to gain extra energy for proliferation. Although oxidative phosphorylation generates more ATP, cancer cells prefer glycolysis as their main source of energy, aka Warburg effect.[9-11] Indeed, inhibition of glycolytic pathways has shown promising results as therapeutics for cancers, such as 2-deoxyglucose (2-DG) etc.[12,13]

Hypoxia-induced factor-1α (HIF-1α) is one of the central regulators of cellular metabolism; HIF-1α integrates with hypoxia-response element (HRE) of target genes and is implicated in almost every aspect of cancer biology: tumor metastasis, angiogenesis, energy metabolism, apoptosis, etc HIF-1α specifically upregulates pathways involved in glycolysis and decreases substrates for aerobic metabolism. HIF-1α is well studied in various types of cancer, including hematopoietic malignancies.[14,15] Echinomycin is a quinoxaline antibiotic, which binds to HRE sequence and acts as a potent HIF-1α inhibitor.[16]

In order to elucidate how systemic chemotherapy affects the metabolism and immune regulation of malignant T cells, we utilized several model systems and patient samples to show that CHOP chemotherapy promotes glycolysis and IL-17 pathways in a HIF-1α-dependent fashion.

2 | METHODS

2.1 | Patient characteristics

Patient registry was from the cutaneous lymphoma clinic and general dermatology clinic, Department of Dermatology, Ruijin Hospital, between 2003 and 2015. The diagnosis of CTCL was based on the criteria of the 2005 WHO-EORTC classifications[1] and staging of CTCL and MF was based on 2007 ISCL/EORTC recommendations.[17]

2.2 | Generation of tumor xenograft mouse model

We generated ex vivo mouse model of CTCL by inoculating $1*10^7$ HH cells subdermally to axillary skin of 4-week-old female BABL/c nude mice. Full-dose CHOP equivalent to human use resulted in significant lethality in mice. Dosage of CHOP regimen was optimized to cyclophosphamide 40 mg/kg, doxorubicin 3.3 mg/kg, vincristine 0.5 mg/kg, prednisone 0.2 mg/kg every week. Once tumor volume reaches 150 mm^3 (10-15 days after inoculation), CHOP regimen was delivered intravenously at weekly basis. In echinomycin-treated group, 30 μg/kg echinomycin was given by intraperitoneal injection every other day starting at same day of CHOP therapy.

2.2.1 | Flow cytometry

Inoculated tumor cells were isolated from xenograft mouse model by passing through a 70-um nylon mesh filter into a 50-mL conical tube. Cells were resuspended in PBS and layered over lymphocyte M to isolate viable lymphocytes. All cell preparations were ACK-lysed and washed before analysis. For surface staining, cells were suspended in PBS with 2% FCS containing Fc Block (50 ng/mL) prior to incubation with fluorochrome-conjugated Abs (anti-human CD4). The stained cells were analysed with a FACSCanto II flow cytometer using FACSDiva software (v6.1.3, Becton Dickinson). Data were analysed using FlowJo software (v9.3.2, TreeStar).

2.2.2 | Cell culture

HH cells (ATCC, CRL-2105) and Hut78 cells (Shanghai Institute of Biochemistry and Cell Biology) were cultured per protocol. CHOP regimen were used at following concentration: cyclophosphamide 27.85 μg/mL, doxorubicin 1.858 μg/mL, vincristine 0.074 μg/mL, prednisone 0.0325 μg/mL. Echinomycin was added to culture media at final concentration of 1.5 nmol/L.

2.3 | RT-PCR

RNA was extracted either from cells or skin biopsy samples using TRIzol® (Life Technologies) and further purified using the RNeasy kit with on-column DNase I digestion (Qiagen). For qPCR, 1 μg of RNA was reverse-transcribed using iScript™. 0.5 μL was used with the SYBR® Green Master Mix, and each reaction was performed in triplicate. qRT-PCR was performed on the Bio-Rad iCycler with MyIQ single colour real-time PCR detection system module with the following parameters: 95°C at 3 minutes, (95°C 10 seconds, 55°C 30 seconds) Å ~ 40, 95°C 1 minute, 55°C 1 minute. The fold change in transcript levels was calculated using the ΔΔCt method. β-actin was used as controls.

2.4 | Primers (5′ to 3′)

HIF1A: CATCTCCATCTCCTACCCACA and CTTTTCCTGCTCTGTTTGGTG.

IL17F: GAAGGTGCTGGTGACTGTTG and CCTGTGAAGTGGA GGGAATT.

STAT3: GGCACCTTCCTGCTAAGATTC and GGTCTTACCGCTGAT GTCCTT.

GLUT1: AGGAGATGAAGGAAGAGAGTCG and TGCTCGTGGAGT AATAGAAGACA.

HK2: CATCTGCTTGCCTACTTCTTCA and ATCTGGAGTGGA CCTCACAAAG.

GPI: ATACCCTGTGACTTCCTCATCC and AATAGAGTTGGTT GGGCGATTT.

PKM: AGTGTGACGAGAACATCCTGTG and AGAGAAATAAGC CCATCATCCA.

ENO1: AAGGGTGTCTCAAAGGCTGTT and TTTTCTGTTCCATC CATCTCG.

LDH: TATGGAGTGGAATGAATGTTGC and CCAGGATGTGTAGC CTTTGAGT.

3 | RESULTS

3.1 | Limited therapeutic effect of CHOP chemotherapy

We retrospectively analysed 18 patients with advanced CTCL (including advanced MF, PTCL and c-ALCL) from registry in Cutaneous Lymphoma Clinic, Department of Dermatology, Ruijin Hospital. We compared the overall survival and duration of response in 9 patients received CHOP chemotherapy and 9 patients received non-chemotherapy (which includes combination of topical corticosteroids, narrow-band UVB and bexarotene). No statistical difference was observed in the distribution of patients between two groups in age and gender. There is no significant difference in overall survival between CHOP and non-chemotherapy groups (log-rank $P = .75$, Figure 1A). However, compared with patient received non-chemotherapy, patient in CHOP group has a significantly decreased duration of response (time in remission, $P = .0034$, log-rank hazard ratio = 3.54, Figure 1B).

3.2 | HIF-1α is upregulated in advanced MF and CHOP chemotherapy

As the initial step to address whether tumor microenvironment is altered by CHOP chemotherapy, we focused on HIF-1α, a master regulator of cellular metabolism. We first measured lesional *HIF1A* expression in early and advanced MF patients. HIF-1α expression was elevated by 2.3-fold in advanced MF (Figure 2A). Mirroring that, HIF-1α upregulation was also observed in HuT78 cells after CHOP treatment, indicating CHOP therapy tunes tumor cells more hypoxic as found in advanced MF (Figure 2B). To examine whether this effect holds true in a more physiological model, we generated tumor xenograft mouse mode: HH cells inoculated in BABL/c nude mice (see Method Section). Indeed, HIF-1α expression is significantly increased when xenograft was treated with CHOP. HIF-1α upregulation is reversible with intraperitoneal injection of echinomycin, a blocking agent of HIF-1α (Figure 2C).

3.3 | CHOP chemotherapy upregulates glycolysis via HIF-1α

Since HIF-1α is a key regulator in cellular metabolism, we sought to investigate the glycolysis pathway by measuring the expression of key enzymes in glycolysis pathway in Hut-78 cell line. Expression of *GLUT1*, *HK2*, *GPI*, *ENO1* and *PKM* (transcripts encode for glucose transporter 1, hexokinase 2, glucose-6-phosphate isomerase, enolase 1 and pyruvate kinase) was significantly upregulated by CHOP in Hut78 cells (Figure 2D). Expression of LDH-α remained unchanged by CHOP. The same upregulation in glycolytic pathways was observed in the xenograft tumor (Figure 2E). Addition of echinomycin completely reversed the increase of glycolytic enzymes in both models, indicating a mediating role of HIF-1α (Figure 2D,E).

3.4 | Increased lesional IL-17F after CHOP treatment

Differentiation of either Treg cells or Th17 cells is dependent of glycolysis and local oxygen concentrations. IL-17F expressing cells were quantified by flow cytometry in inoculated tumors. Single dose of CHOP infusion significantly increased lesional IL-17F positive cells (Figure 3A-C). Serum IL-17F was measured in 50 MF patients including 20 early MF (stages I and IIa) and 30 advanced MF (stages IIb, III and IV). A large number of patients with advanced MF had elevated circulating IL-17F (Figure 3D).

In Hut78 cell line and xenograft tumor model, IL-17F transcript level was upregulated by CHOP, recapitulating the in vivo findings. Expressions of HIF-1α, Stat3 and RORγT were also increased by CHOP, further elucidating the mechanism of IL-17F upregulation. The upregulation was blocked by echinomycin, thus suggesting a key regulatory role of HIF-1α (Figure 4A,B).

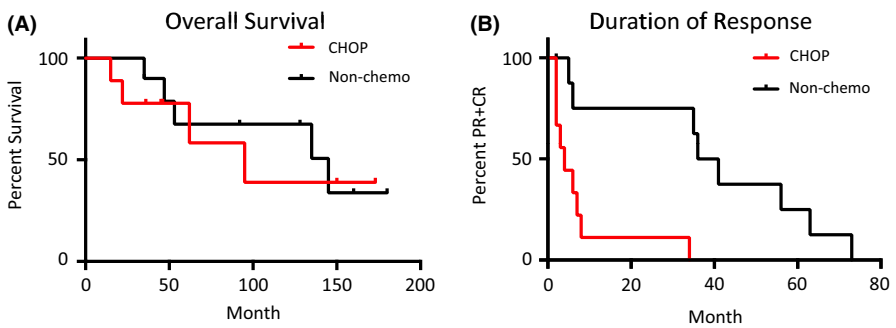

FIGURE 1 Limited therapeutic effect of CHOP chemotherapy in advanced CTCL. Kaplan-Meier plot of patients overall survival (A) and duration of response (B) between CHOP chemotherapy and non-chemotherapy groups. Nine advanced CTCL patients were included in each group

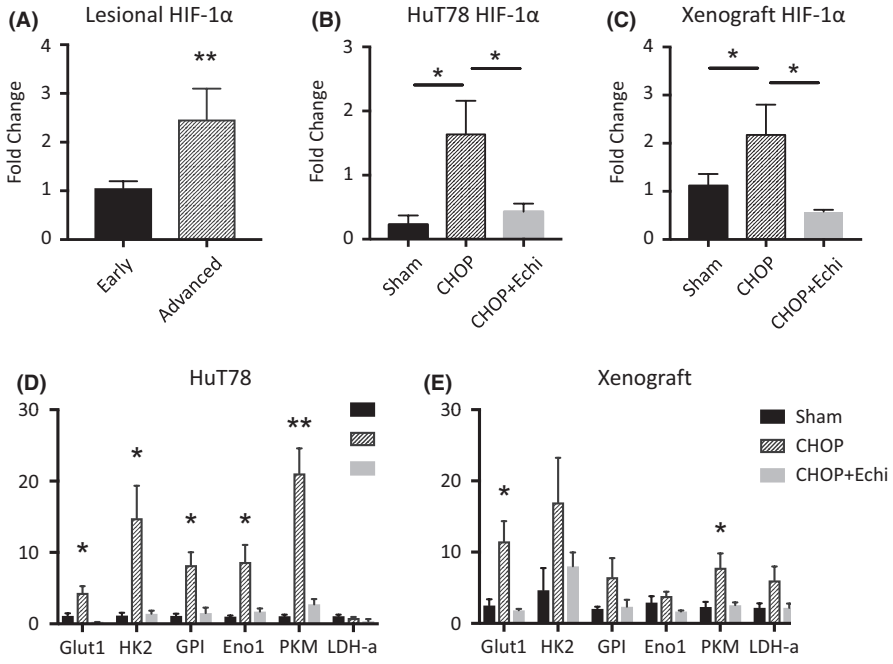

FIGURE 2 CHOP chemotherapy promotes tumor cell glycolysis via HIF-1α. *HIF1A*mRNA levels were measured by real-time PCR in skin biopsy samples from lesional skin of early MF (n = 7) and advanced MF (n = 10) (A), cell lysates of HuT78 cells with treatment of CHOP and echinomycin (n = 5) (B) and xenograft tumor with treatment of CHOP and echinomycin (n = 4)(C). (D, E) After treatment with CHOP or CHOP + echinomycin, RNA was isolated from Hut78 cells or xenograft tumors and used for real-time PCR analyses of glycolytic enzymes. Expression levels in sham group were set to 1. Results are normalized to β-actin transcript levels. n = 4. All graphs show means ± SEM;**P* < .05;***P* < .01

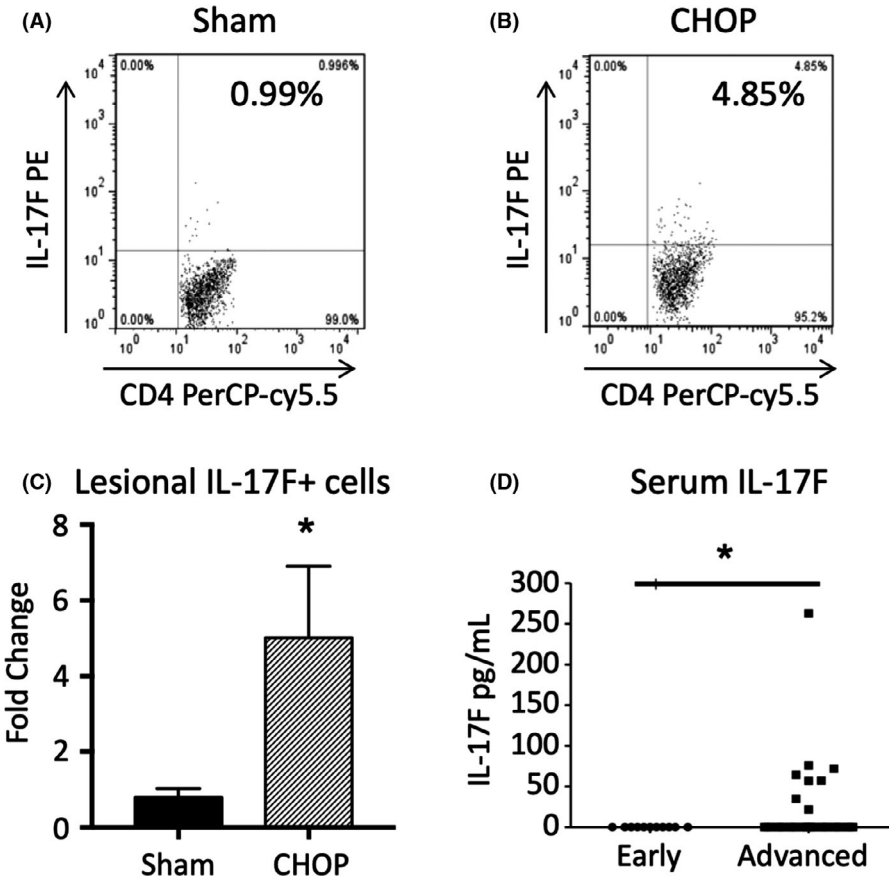

FIGURE 3 Increased lesional IL-17F after CHOP treatment. (A,B)Sorted Th17 cells ($CD4^+$, $CD17F^+$) from xenograft mouse models after treatment with Sham or CHOP regimen. C, Quantification of IL-17F positive cell numbers in panel A and B, n = 3. (D) Serum IL-17F protein level was quantified by ELISA in patients with early-stage MF and advanced stage MF. All graphs show means ± SEM;**P* < .05. n = 5

3.5 | Therapeutic effect of HIF-1α inhibition in CTCL xenograft model

In order to investigate whether HIF-1α inhibition has therapeutic effect toward advanced CTCL, we tested in tumor xenograft mouse model. In this model, weekly CHOP infusion was administered when tumor volume reached 150 mm^3, after 20 days of weekly infusion, tumor size was significantly reduced (Figure 4C). It is worth mentioning that such significant difference was no longer observed after 40 days, mirroring the limited long-term therapeutic effect of

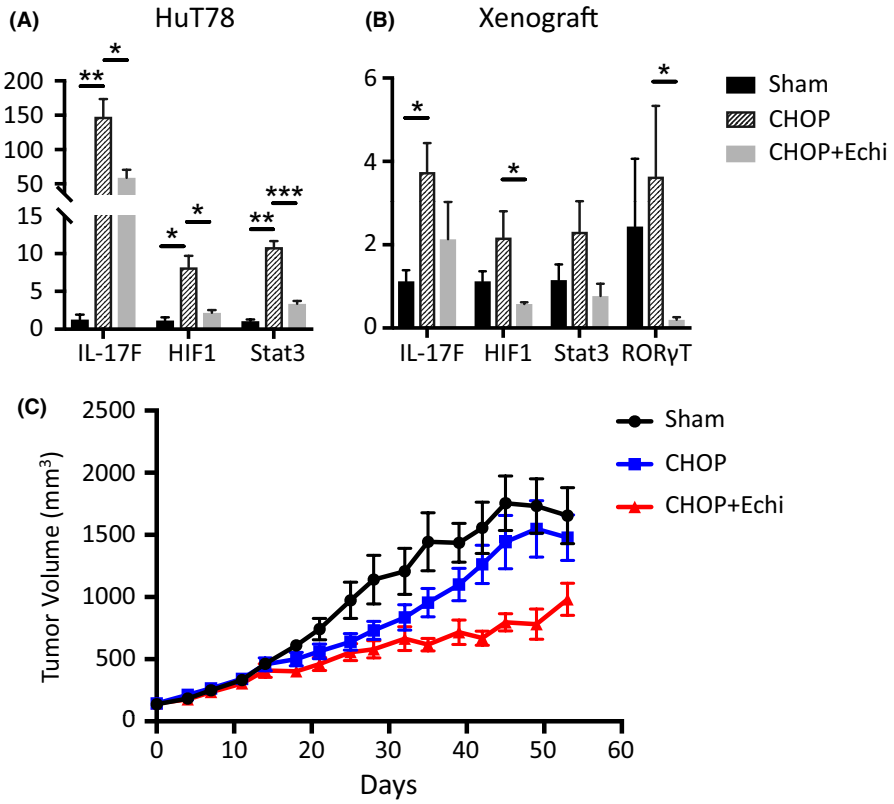

FIGURE 4 Therapeutic effect of HIF-1α inhibition in CTCL xenograft model. (A,B) mRNA levels of *IL17F* and its regulatory genes: HIF1A, STAT3 and RORγT were measured by qRT-PCR in HuT78 cells and xenograft tumor with treatment of sham, CHOP or CHOP + echinomycin. Results are normalized to β-actin transcript levels. n = 5. C, Xenograft tumor volume (mm^3) of mice receiving intraperitoneal injections of Sham treatment (black), CHOP regimen (blue) and CHOP plus echinomycin treatment (red). All graphs show means ± SEM; ns, not significant; $^*P < .05$;$^{**}P < .01$; $^{***}P < .001$. n ≥ 8

chemotherapy in advanced CTCL. During CHOP therapy, 30ug/kg echinomycin was delivered intraperitoneally once every two days to block HIF-1α. Compared with CHOP regimen, combination of echinomycin and CHOP showed a more significant reduction of tumor sizes starting at the third week. Such reduction is persistent toward the 53rd day (Figure 4C).

4 | DISCUSSION

In summary, our study suggests that CHOP chemotherapy alters tumor cell glycolysis and IL-17 pathways via HIF-1α. We provided potential mechanisms of how systemic chemotherapy failed to achieve satisfactory efficacy in advanced CTCL and often leads to tumor recurrence.

In patients with advanced CTCL, CHOP chemotherapy leads to rapid tumor regression, and however, the duration of response is significantly inferior to other canonical treatments. Consistent with published studies, CHOP chemotherapy resulted in similar overall survival with non-chemotherapy treatments. By using two different model systems, HuT78 and tumor xenograft mouse models, we confirmed upregulation of HIF-1α after CHOP treatment, which is the same change in advanced CTCL. It suggested that CHOP chemotherapy tunes the tumor in the same manner as in aggressive CTCL, altering gene expressions by upregulating HIF-1α, hence provided rationale of limited efficacy and increased tumor recurrence of CHOP chemotherapy in CTCL.

After CHOP chemotherapy and in advanced CTCL, a vicious cycle is created where CTCL microenvironment becomes more hypoxic, continuous HIF-1α activation drives malignant T cells toward Th17 phenotype. Previous studies revealed that malignant T cells can have a Th17 phenotype and induce expression of angiogenic factor and MMPs to promote tumor growth.[18,19] IL-17F expression correlates with progressive diseases and worse clinical outcomes. The increase of IL-17F during CHOP chemotherapy is HIF-1α-dependent; supporting that Th17 phenotype is a downstream effect of hypoxia. In our study, IL-17 expression is induced by Stat3 and RORγT, the same mechanism with other published studies[18,20-22]: Stat3 inhibition decreases proliferation and increased survival of CTCL tumor cells in vitro. Mouse model carrying activated form of Stat3 showed significant increase of IL-17 and IL-22 producing T cells. Since all the above downstream effect of HIF-1α activation promotes tumor growth and invasion, we utilized xenograft model to reveal the therapeutic effect of HIF-1α inhibitor in CTCL mouse model.

Echinomycin is a quinoxaline antibiotic, which has showed its therapeutic potentials in a plethora of cancers such as haematological malignancies, lung cancer and soft tissue sarcomas.[23,24] Besides echinomycin, many anti-cancer medications including digoxin and bortezomib showed anti- HIF-1α activities.[25]

In conclusion, CHOP chemotherapy alters tumor cell metabolism through HIF-1α, same mechanism in aggressive CTCL; altering glycolysis and IL-17 pathways. Our data provided evidence for the limited efficacy of CHOP chemotherapy in CTCL and showed HIF-1α

blockade is promising as a synergic agent with systemic chemotherapy for patients with advanced CTCL.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

K. Li and X. Shen performed the research. J. Zheng, X. Shen and H. Wang designed the research study. X. Shen, K. Li and B. Wang analysed data. H. Wang contributed essential experimental guidance. B. Wang wrote the paper.

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How to cite this article: Wang B, Li K, Wang H, Shen X, Zheng J. Systemic chemotherapy promotes HIF-1α-mediated glycolysis and IL-17F pathways in cutaneous T-cell lymphoma. *Exp Dermatol.* 2020;29:987–992. https://doi.org/10.1111/exd.14133