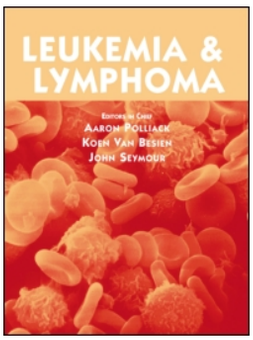

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

Effect of leucovorin administration on mucositis and skin reactions in patients with peripheral T-cell lymphoma or cutaneous T-cell lymphoma treated with pralatrexate*

Francine M. Foss, Terri L. Parker, Michael Girardi & Anlong Li

To cite this article: Francine M. Foss, Terri L. Parker, Michael Girardi & Anlong Li (2019): Effect of leucovorin administration on mucositis and skin reactions in patients with peripheral T-cell lymphoma or cutaneous T-cell lymphoma treated with pralatrexate*, Leukemia & Lymphoma, DOI: 10.1080/10428194.2019.1612061

To link to this article: https://doi.org/10.1080/10428194.2019.1612061

Published online: 23 May 2019.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2019.1612061

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Effect of leucovorin administration on mucositis and skin reactions in patients with peripheral T-cell lymphoma or cutaneous T-cell lymphoma treated with pralatrexate*

Francine M. Foss[a], Terri L. Parker[a], Michael Girardi[b] and Anlong Li[c]

[a]Department of Hematology, School of Medicine, Yale University, New Haven, CT, USA; [b]Department of Dermatology, School of Medicine, Yale University, New Haven, CT, USA; [c]School of Medicine, Yale University, New Haven, CT, USA

ABSTRACT

Peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL) are rare, heterogeneous non-Hodgkin lymphomas with poor prognoses. Pralatrexate has demonstrated efficacy in T-cell lymphomas; however, mucositis has been reported as the most common dose-modifying adverse event. Leucovorin has been shown to minimize mucositis incidence, without sacrificing pralatrexate efficacy. We retrospectively studied 34 patients (7-PTCL/27-CTCL) treated with pralatrexate alone or pralatrexate and leucovorin. Leucovorin was administered preemptively prior to any mucositis occurrence. Pralatrexate dosing ranged from 10–30 mg/m^2 and clinical response or disease stabilization was observed in 85.2%. The incidence of mucositis was reduced in CTCL patients to 17% and was ameliorated in all but one patient with PTCL. There was no change the incidence of skin reactions with the addition of leucovorin. The response rates were similar to those previously reported in CTCL and PTCL. The addition of leucovorin reduced the incidence of mucositis in patients with CTCL and PTCL.

ARTICLE HISTORY
Received 18 December 2018
Revised 18 March 2019
Accepted 15 April 2019

KEYWORDS
Mucositis; peripheral T-cell lymphoma; cutaneous T-cell lymphoma; leucovorin; pralatrexate; skin reactions

Introduction

T-cell lymphomas are a broad collection of heterogeneous diseases, comprising 10% to 15% of all non-Hodgkin lymphomas in the United States; ~5000 to 6000 cases annually [1,2]. T-cell lymphomas are further categorized into peripheral (PTCL) and cutaneous T-cell lymphomas (CTCL). PTCL and CTCL are separated by their diagnostic, phenotypic, molecular, and prognostic characteristics. PTCL is rare and aggressive and develops from mature post-thymic T-cells or natural killer cells [3]. CTCLs tend to appear on the skin, due to the expression of the cutaneous lymphocyte antigen, and in most cases, tend to be indolent. However, in the advanced stage, CTCL will behave similarly to PTCL, requiring equally aggressive systemic treatment [4]. Achieving durable clinical responses in PTCL or advanced-stage CTCL are a challenge for clinicians and prognoses remain poor. Additionally, oral and gastrointestinal mucositis and/or skin reactions are frequent toxicity complications of PTCL and CTCL treatment, leading to significant morbidity, decreased quality of life, and early discontinuation of active therapy. Despite the frequency of mucositis and skin reactions, no standard medical management strategy exists, with the exception of treatment modification, dose reduction or discontinuation, despite notable responses to treatment.

The PROPEL study, a Phase II trial of pralatrexate monotherapy in relapsed or refractory PTCL, demonstrated a durable clinical benefit (objective response rate of 29%) [5]. Within the PROPEL cohort, the majority of patients tolerated the target dose of 30 mg/m^2 weekly, for the duration of treatment, 6 weeks of a 7-week cycle, however, 68% had one or more dose omissions due to adverse events. The most common reason for dose reduction was mucositis, which occurred in 23% of patients. Despite vitamin supplementation of B_{12} 1 mg intramuscularly every 8 to 10 weeks and daily oral folic acid 1.0 to 1.25 mg to attempt to ameliorate mucositis in the trial, 71% of patients experienced some grade of mucositis. Skin reactions included rash and pruritus and were observed in 15% and 14% respectively [5].

Leucovorin administration has been used as standard rescue for patients receiving high dose methotrexate therapy and has recently been studied in patients

CONTACT Francine M. Foss francine.foss@yale.edu Yale Cancer Center, Yale-New Haven Hospital, 20 York Street, New Haven, CT 06510, USA
*Research was conducted at: Yale Cancer Center, Yale-New Haven Hospital, 20 York Street, New Haven, CT, 06510, USA.

with PTCL and CTCL receiving pralatrexate. Haddad conducted an observational study of 17 PTCL patients with grade 2+ mucositis and were given 25 mg leucovorin every six hours, for the first five days of a week prior to pralatrexate treatment [6]. This author found that with this reactive regimen to existing mucositis, rather than preemptive initiation prior to its occurrence, no patients discontinued pralatrexate treatment due to mucositis and there was no decline in clinical response [6]. Koch et al. presented the findings of preemptive leucovorin administration in three patients with CTCL that received 50 mg leucovorin intravenously, 24 hours after pralatrexate. They reported a good clinical response and no occurrence of dose-limiting mucositis [7].

Our aim was to report the potential benefit of preemptive leucovorin administration in reducing mucositis and skin reactions for PTCL and CTCL patients receiving treatment with pralatrexate.

Methods

We conducted a retrospective chart review of patients that had received either pralatrexate and leucovorin, or pralatrexate alone, at the Yale Cancer Center between 2011 and 2015.

Patients that had received one or more doses of pralatrexate for systemic treatment of PTCL or CTCL were included in the review. Those patients that received treatment prior to 2013 received pralatrexate alone, while those treated in 2013 and later, received pralatrexate and leucovorin. There were no other notable differences in care during the review period. All occurrences of any grade of mucositis were recorded and skin reactions were identified as a new rash or increase in pruritus by one grade.

Results

Pralatrexate dosing ranged from 10–30 mg/m^2, either weekly for three weeks of every 28 days, or every other week and patients also received the recommended supplementation of intramuscular B_{12} and oral folic acid. For patients that received pralatrexate and leucovorin, 50 mg of leucovorin was administered orally, every six hours for four doses, the day following pralatrexate treatment based on an earlier study by Koch et al.

Thirty-four patients (17 female:17 male, median age 54yrs (range 27-89), 7 PTCL:27 CTCL) were identified and included in the review (Table 1). Twenty-four patients received pralatrexate alone, while 10 received leucovorin in addition to pralatrexate treatment (9 CTCL/1 PTCL). The mean number of pralatrexate cycles was 7 (range 2–18).

In the group who received pralatrexate alone, eight patients (33%), 1-PTCL/7-CTCL, reported mucositis which was Grade 1 or 2 as shown in Table 1. Only one patient experienced mucositis in the group receiving leucovorin with pralatrexate on cycle 1. In addition, there were 3 patients who developed mucositis in cycle 1 and were administered leucovorin at 50 mg every 6 hours for four doses on the day following pralatrexate on cycle 2 and on subsequent cycles. Mucositis albeit mild, recurred in one patient but 2 had no further mucositis. Pralatrexate dose was able to be escalated in all three to best clinical response. Mucositis most often developed on the first cycle of therapy in the patients who did not receive leucovorin. Doses of pralatrexate were held until resolution of mucositis and then reinstituted. Dose escalation in this retrospective cohort was determined by patient tolerance to drug and ongoing clinical effect observed, and doses were able to be escalated in most patients.

Skin reactions in the form of erythema of existing CTCL lesions and diffuse macular rashes occurred in one (17%) PTCL patient and 15 CTCL patients. The frequency of skin rash was similar in patients with CTCL who did not receive leucovorin (53%) and those who did (55%), as shown in Table 1. Clinical response (partial or complete) determined by MSwAT to be CR or PR was observed in 13 of 27 CTCL patients and five of seven PTCL patients. As shown in Table 1, there was no difference in response rates between the patients receiving leucovorin and those who had no leucovorin although there was a trend toward a higher response in the leucovorin patients. Given the small number of patients, it is difficult to determine the significance of this difference. Of the six patients who had PD, four had received leucovorin, while two had not.

Discussion

Balancing the safety and effectiveness of cancer therapy can be challenging, as adverse events can lead to dose modification or discontinuation, prohibiting the use of effective treatments. In a Phase II registration trial of pralatrexate in patients with peripheral T-cell lymphomas, the most frequently occurring toxicity was mucositis, despite aggressive supportive care measures and vitamin B12 and folate supplementation. Here, we have presented our experience using leucovorin with pralatrexate in patients with PTCL or

Table 1. Summary of CTCL and PTCL patients, treatments and outcomes.

Patient	Diagnosis	Stage	Pralatrexate dose (mg/m^2)	Response	Leucovorin	Mucositis	Skin flare
1	CTCL	IVA	12	PR	Yes	No	No
2	CTCL	IV	15, 20	PR	From C2	Gr 2 (cycle1), none after cycle2	No
3	CTCL	IIB	22.25, 30	PR	Yes	No	Yes
4	CTCL	IIB	10, 12	PR	From C2	Gr 2 (cycle1), none after cycle2	Yes
5	CTCL	III	15, 12	SD	From C2	Gr 2 (cycle 1) , Gr 1 after cycle 2	Yes
6	CTCL	IVA	15	PD	Yes	No	Yes
7	CTCL	IVA	10, 12, 15, 20	SD	Yes	No	Yes
8	CTCL	IIB	15	PR	Yes	No	Yes
9	CTCL	IVA	15	CR	Yes	No	No
10	CTCL	IIB	10	PD	Yes	No	Yes
11	CTCL	IIB	10	PD	Yes	No	Yes
12	CTCL	IIB	15	CR	Yes	Gr 1	No
13	CTCL	IV	15	PR	No	No	No
14	CTCL	IV	10, 20, 30	PR	No	No	Yes
15	CTCL	IV	12	SD	No	Gr 2	No
16	CTCL	IIA	10, 12, 15, 20, 30	PR	No	No	No
17	CTCL	IIB	15	PR	No	Gr 2	No
18	CTCL	IIA	15	SD	No	No	Yes
19	CTCL	tIB	15	SD	No	No	Yes
20	CTCL	IIB	12, 17	SD	No	Gr 2	Yes
21	CTCL	IIB	10, 15	PD	No	Gr 1	No
22	CTCL	III	10	PR	No	No	Yes
23	CTCL	IV	12, 15, 20	SD	Yo	Gr 1	No
24	CTCL	IV	12	PR	No	No	Yes
25	CTCL	III	12, 25	SD	No	Gr 2	No
26	CTCL	IIB	15	SD	No	No	Yes
27	CTCL	IVA	12	SD	No	No	Yes
	PTCL-Nos	IV	12, 20, 14	PR	No	Gr 2	No
29	PTCL-Nos	IV	15	SD	No	No	No
30	PTCL-Nos	IV	10	CR	No	No	No
31	PTCL-Nos	IV	15, 10, 5	NR	No	Gr 2	Yes
32	PTCL-Nos	IV	15	PR	No	No	No
33	PTCL-Nos	IV	15, 20	NR	Yes	No	No
34	ALCL	III	15, 12	SD	No	No	Yes

CTCL: cutaneous T-cell lymphoma; PTCL: peripheral T-cell lymphoma; NOS: not otherwise specified; ALCL: anaplastic large cell lymphoma.

CTCL and demonstrate a reduction in the overall incidence of mucositis to 17% in patients with CTCL.

In our series, a number of our patients were treated with pralatrexate at doses less than the approved dose of 30 mg/m^2 weekly for 6 weeks. A Phase I/II study of pralatrexate by Horwitz et al demonstrated response in CTCL patients at a lower dose (up to 15 mg/m^2) and on schedules including weekly x3 every other week. Horwitz et al. reported an overall incidence of mucosal inflammation of 43% in patients who received doses $\leq$15 mg/m^2, similar to our patients, with no dose-response relationship for toxicity at the lower doses. Horwitz did find that only 21% of their patients experienced skin toxicity, whereas in our experience, 15 of 27 CTCL patients had a skin flare. The definitions of skin flare may be different between studies and in the Horwitz study conducted earlier, skin flare was not defined and skin reactions included new skin rashes. We observe that skin flare occurs frequently in patients with CTCL who are receiving pralatrexate and that, unlike mucositis, there was no reduction in skin flare with preemptive leucovorin administration.

The dosing of leucovorin has differed among studies. Our patients received 50 mg of leucovorin, administered orally, every six hours for four doses, the day following pralatrexate treatment. This dose was extrapolated from a report by Koch et al. who administered preemptive leucovorin, however, as a single 50 mg intravenous infusion, 24 hours following pralatrexate [7]. In another series, Haddad treated PTCL patients with 25 mg orally every six hours for five days the week of pralatrexate therapy as a reactive intervention to existing mucositis, rather than preemptively before its occurrence [6]. Based on these existing data, the minimal dose of leucovorin to ameliorate mucositis is unknown but may range from 25–50 mg.

Because many of our patients were treated at doses lower than the approved dose of 30 mg/m^2 for PTCL patients and on different schedules, it is difficult to compare responses in our series to published data. The majority of CTCL patients were treated at lower doses based on the data of Horwitz et al., and there was variability in dosing over the course of treatment. We noted that 4 of 5 (80%) patients with CTCL who received doses less than 15 mg/m^2 had a response as did 3 of 7 (42%) with PTCL. In the PROPEL trial of relapsed and refractory PTCL patients treated with pralatrexate, the response rate was 29%

[5]. For our CTCL patients, a response rate of 48% (13/27) was achieved, although when response and disease stabilization were combined, the rate improved to 85.2% (23/27). Horwitz reported that in their cohort of CTCL patients, a dose of 15 mg/m^2/week for 3/4 weeks elicited a response rate of 45% [3].

In summary, we demonstrate in this retrospective series that the addition of leucovorin to pralatrexate is effective in reducing the incidence of mucositis in patients with PTCL and CTCL. A prospective clinical trial with a larger number of patients is ongoing to confirm these findings.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at https://doi.org/10.1080/10428194.2019.1612061.

References

[1] Savage KJ, Chhanabhai M, Gascoyne RD, et al. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Ann Oncol. 2004;15:1467–1475.

[2] The NHL Classification Project. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood. 1997;89:3909–3918.

[3] Horwitz SM. Management of peripheral T-cell non-Hodgkin's lymphoma. Curr Opin Oncol. 2007;19:438–443.

[4] Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010;28:4730–4739.

[5] O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol. 2011;29:1182–1189.

[6] Haddad PA. Efficacy of short oral leucovorin rescue (SOLR) in managing recurrent pralatrexate (Folotyn) induced mucositis (RPIM) despite dose reduction. ASH Annual Meeting Abstracts. Blood. 2011;118:4745.

[7] Koch E, Story SK, Geskin LJ. Preemptive leucovorin administration minimizes pralatrexate toxicity without sacrificing efficacy. Leuk Lymphoma. 2013;54:2448–2451.