

Submitted by:

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NCCN Guidelines Panel:

On behalf of Acrotech BioPharma LLC, I respectfully request the NCCN T-Cell Lymphoma Guideline Panel consider adding mention of the use of leucovorin as prophylaxis for pralatrexate-induced mucositis as a section within the Supportive Care section of the guidelines.

Specific Changes: Short review within LYMP-B section as Mucositis Associated with Pralatrexate, that post-pralatrexate dose administration of leucovorin could be considered as a way in which to reduce the mucositis adverse events associated with use of pralatrexate for relapsed/refractory PTCL.

Rationale: Pharmacologic rationale, preclinical studies, and clinical evidence suggest that leucovorin may reduce the incidence of oral mucositis toxicity of pralatrexate (71% overall; 8% G3; 4% G4) observed in clinical trials and noted in the product label.^{1,2,3}

Two preclinical studies concluded that due to the high therapeutic index of pralatrexate relative to methotrexate, modest doses of LV administered over short intervals may abrogate the pralatrexate mucositis AE without diminishing its therapeutic efficacy.^{4,5}

Two retrospective reviews of short-course leucovorin administered 24hr after a pralatrexate dose reported a significant reduction in incidence of oral mucositis as compared to that reported in the pralatrexate label.^{6,7}

A prospective, single-arm, multicenter, Phase 2 clinical trial was conducted to determine the effect of leucovorin in reducing pralatrexate-related oral mucositis in patients with hematologic malignancy, including PTCL and CTCL (NCT02106650).⁸ Study treatment consisted of pralatrexate 30mg/m² once weekly for 6 weeks followed by one week of rest, for two 7-week cycles. Leucovorin was self-administered orally at 25mg TID for two consecutive days (total of 6 doses), starting 24 hours after each dose of pralatrexate. All patients received vitamin B12 and folic acid supplementation as per product label. Use of oral leucovorin 24 hours after pralatrexate infusion resulted in a significant reduction in the incidence of oral mucositis: no patient reported ≥G3 oral mucositis, and no patient omitted, delayed or reduced pralatrexate dose due to oral mucositis. Two patients (2/35; 5.7%) reported G2 oral



mucositis (95% CI=1-19%). Grade 1 oral mucositis was reported in 4 patients (4/35; 11%) resulting in a 17% (6/35) overall incidence of oral mucositis in Cycle 1.

Thank you for your consideration.

Sincerely,



Mark Acosta, PharmD

1. Folutyn [package insert 5/2020] Acrotech Biopharma LLC, East Windsor, NJ
2. O'Connor OA, Horwitz S, Hamlin P, et al. A phase '2-1-2' study of two different doses and schedules of pralatrexate, a high affinity substrate for the reduced folate carrier (RFC-1), in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. J Clin Oncol 2009, Sept 10;27(26):4357-4364
3. 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; 29:1182-9.
4. Visentin M., Unal ES, Goldman ID. The impact of 5-formyltetrahydrofolate on the anti-tumor activity of pralatrexate, as compared to methotrexate, in HeLa cells in vitro. Cancer Chemother Pharmacol 2014; 73:1055-1062.
5. Tedeschi PM, Kathari YK, Farooqi IN, Bertino JR. Leucovorin rescue allows effective high-dose pralatrexate treatment and an increase in therapeutic index in mesothelioma xenografts. Cancer Chemother Pharmacol 2014; Nov;74(5):1029-1032.
6. Koch E, Story SK, Geskin LJ. Preemptive leucovorin administration minimizes pralatrexate toxicity without sacrificing efficacy. Leuk Lymphoma. 2013;54:2448-51.
7. Foss FM, Parker TL, et al. Effect of leucovorin administration on mucositis and skin reactions in patients with peripheral T-cell lymphoma or cutaneous T-cell lymphoma treated with pralatrexate. Leuk Lymphoma 2019 Dec;60(12):2927-2930
8. Shustov AR, Shinohara MM, Dakhil SR, Bhat G, Zain JM. Management of Mucositis with the Use of Leucovorin as Adjunct to Pralatrexate in Treatment of Peripheral T-Cell Lymphomas (PTCL) – Results from a Prospective Multicenter Phase 2 Clinical Trial. Blood 2018 132:2910 (Abstract 2910 with poster data update).

