Pralatrexate with Vitamin Supplementation in Patients with Previously Treated, Advanced Non-small Cell Lung Cancer

Safety and Efficacy in a Phase 1 Trial

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Introduction: Pralatrexate is an antifolate designed for preferential tumor cell uptake and accumulation and received accelerated Food and Drug Administration approval in relapsed/refractory peripheral T-cell lymphoma. Pralatrexate 135 to 150 mg/m^2 every 2 weeks without vitamin supplementation was active in non-small cell lung cancer (NSCLC) although mucositis was dose limiting. This phase 1 study evaluated the safety of higher pralatrexate doses with vitamin supplementation to minimize toxicities.

Methods: Patients with stage IIIB/IV NSCLC received pralatrexate 150 to 325 mg/m^2 every 2 weeks with folic acid and vitamin B_{12} supplementation. Outcomes measured included adverse events (AEs), pharmacokinetics, and radiologic response.

Results: Thirty-nine patients were treated for a median of two cycles (range 1–16+). Common treatment-related grade 3 and 4 AEs by dose ($\leq$190 mg/m^2 and $>$190 mg/m^2) included mucositis (33 and 40%) and fatigue (11 and 17%). Treatment-related serious AE (SAE) rates for doses $\leq$190 and $>$190 mg/m^2 were 0 and 20%, respectively. The response rate was 10% (95% confidence interval: 1–20%), including two patients with complete response (26+ and 32+ months) and two with partial response. Serum pralatrexate concentrations increased dose dependently up to 230 mg/m^2.

Conclusions: Pralatrexate with vitamin supplementation was safely administered to patients with previously treated NSCLC, and durable responses were observed. The recommended starting dose for phase 2 is 190 mg/m^2. A similar safety profile was observed in patients treated at 230 mg/m^2, although a higher serious AE rate was evident. Mucositis remains the dose-limiting toxicity of pralatrexate, and this study failed to demonstrate that vitamin supplementation prevents mucositis and failed to identify clinical predictors of mucositis. Individualized dose-modification strategies and prospective mucositis management will be necessary in future trials.

Key Words: Pralatrexate, Antifolate, Non-small cell lung cancer, NSCLC, Dose-finding.

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Pralatrexate (FOLOTYN Allos Therapeutics, Inc., Westminster, CO) is an antifolate-targeting dihydrofolate reductase (DHFR) and has a high affinity for the reduced folate carrier (RFC)-1.[1] RFC-1 is highly expressed on malignant tissues and it regulates the internalization of natural folates required for purine and pyrimidine biosynthesis.[2] In lymphoma cell lines, RFC-1 gene expression predicted the antitumor activity of pralatrexate,[3] and it is hypothesized that the high affinity of pralatrexate for RFC-1 leads to selective tumor cell accumulation. Pralatrexate is an efficient substrate for polyglutamylation by the enzyme folylpolyglutamyl synthetase (FPGS), with activity at FPGS greater than that of other antifolates (methotrexate, edatrexate, and aminopterin).[1] The increased uptake and increased polyglutamylation associated with pralatrexate have been shown to correlate with increased tumor growth inhibition in non-small cell lung cancer (NSCLC) xenograft models.[4]

Pralatrexate recently received accelerated approval by the U.S. Food and Drug Administration for the treatment of relapsed or refractory peripheral T-cell lymphoma based on the results of the PROPEL study.[5] Pralatrexate has also been studied in other types of lymphomas and solid tumors.[6] In particular, several studies have evaluated pralatrexate in patients with NSCLC as either monotherapy,[7,8] or in combination with taxanes.[9] Pralatrexate monotherapy was active at doses of 135 to 150 mg/m^2 every 2 weeks (q2w).[7,8] Mucositis was a common dose-limiting toxicity (DLT), but early monotherapy studies did not include administration of vitamin B_{12}

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and folic acid. In the phase 1 study of pralatrexate in combination with a taxane, mucositis was the most common DLT. Supplementation of vitamin B_{12} and folic acid in some patients reduced the incidence of mucositis and allowed the use of increased doses of pralatrexate.[9] In addition, data from studies of the antifolate pemetrexed (ALIMTA) have led to the routine administration of vitamin supplementation with this agent.[10] The objective of this phase 1 study (PDX-007) was to evaluate the safety, tolerability, pharmacokinetic (PK) profile, and optimal dose of pralatrexate with routine vitamin B_{12} and folic acid supplementation in patients with advanced, previously treated NSCLC.

PATIENTS AND METHODS

Study Design

This was a phase 1, nonrandomized, multicenter, dose-escalation study. Study participants were 18 years or older and had stage IIIB or IV NSCLC that was not potentially curable by standard chemotherapy, radiotherapy, or surgical procedures. Other inclusion criteria were at least one prior chemotherapy regimen, Karnofsky Performance Status $\leq$70%, life expectancy more than 3 months, and adequate hematologic, hepatic, and renal function. Key exclusion criteria were previous exposure to pralatrexate, diagnosis of another active concurrent malignancy, clinically significant pleural effusion or ascites, grade 3 or 4 edema, prior pneumonectomy, recent (within 2 weeks of enrollment) radiation therapy or chemotherapy (erlotinib or gefitinib within 1 week before enrollment), symptomatic central nervous system metastases, and other serious medical conditions. The study was conducted in accordance with the principles contained in the Declaration of Helsinki and was approved by the Institutional Review Boards at participating centers. Each patient provided written informed consent to participate.

Treatment

Each patient received pralatrexate intravenously (IV) once q2w. Each cycle of therapy was 4 weeks and consisted of two doses of pralatrexate. Patients received vitamin supplementation starting at least 7 days (day 7) before the first dose of pralatrexate and continued until discontinuation of pralatrexate. Vitamin supplementation consisted of vitamin B_{12} (1 mg intramuscular every 8 to 10 weeks) and folic acid (1 mg orally once daily).

Patients were enrolled sequentially into two treatment groups during the study: treatment group A followed by group B. treatment group A determined the maximum tolerated dose (MTD) of pralatrexate with vitamins based on a modified, accelerated titration method for dose escalation.[11] Treatment group B was a dose de-escalation phase to determine the recommended phase 2 dose using stricter DLT criteria. This phase followed a standard 3 + 3 method of enrollment into each cohort.

The first dose cohort in treatment group A was 150 mg/m^2 q2w by IV bolus (3–5 minutes). If no DLT was observed in the first patient after one cycle of therapy (two doses over 4 weeks), the next patient was enrolled at the next dose level (40 mg/m^2 increments until 270 mg/m^2 and 20% increments thereafter). If a DLT was observed in the first patient, five additional patients were enrolled in the cohort. If only the first patient in the cohort had a DLT after expansion to six patients, dose escalation continued to the next level. If $\geq$2 patients had a DLT with cohort expansion, dose escalation was stopped, and the MTD was defined as the previously tolerated dose. After the MTD was identified, the MTD cohort was expanded to include 16 patients in total to gain additional safety and tolerability experience at that dose level.

Because several patients in the expanded MTD cohort had mucositis as DLT at 270mg/m^2, additional cohorts were enrolled into treatment group B to evaluate lower doses. In addition, $\geq$grade 2 mucositis was added to the DLT definition. Another investigation undertaken in treatment group B was to evaluate the PK and safety profile in patients who received a protracted infusion (more than 60 minutes) of pralatrexate. To further evaluate if the safety profile may be improved using a longer infusion, subsequent cohorts in treatment group B received pralatrexate 230 mg/m^2 q2w by IV bolus, prolonged infusions, and/or lower doses of pralatrexate (40 mg/m^2 reductions).

Treatment was delayed in patients with active mucositis. Those patients who experienced grade 3 mucositis restarted pralatrexate at a 40% reduced dose after mucositis resolved. There was no change in dose for other nonhematologic grade 0 to 2 adverse events (AEs). The dose was delayed for 2 weeks in patients with other grade 3 nonhematologic treatment-related AEs and restarted as follows: if the AE resolved to grades 0 and 1, treatment was restarted at the same dose; if resolved to grade 2, treatment was restarted with a 20% dose reduction; if grade 3 persisted, the next dose was omitted. Pralatrexate treatment was discontinued for any grade 4 treatment-related nonhematologic AE. For treatment-related hematologic AEs, pralatrexate treatment was delayed in patients with grade 2 neutropenia and grade 2 thrombocytopenia. Treatment was delayed and could be restarted at a 20% reduced dose in patients with grade 3 neutropenia with fever or grade 4 neutropenia upon recovery. Prophylactic use of hematopoietic growth factors during cycle 1 was not permitted.

Assessments

Investigators recorded each AE including its relationship to pralatrexate treatment and its severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events scale, Version 3.0. Blood samples were tested for red blood cell (RBC) folate, homocysteine (HC), and methylmalonic acid (MMA) levels at enrollment, before the first dose of pralatrexate, and after cycle 1 as a measure of vitamin deficiency and to measure the impact of vitamin supplementation. Serial PK plasma and urine samples were collected for 72 hours after the first dose of pralatrexate. Additional PK plasma samples were collected for 20 minutes after the second dose. If specimens were available, formalin-fixed paraffin-embedded (FFPE) tumor tissue was collected as part of the treatment initiation visit. Available FFPE tissue was tested for components of folate metabolism (RFC-1, DHFR, FPGS, thymidylate synthase [TS], glycinamide ribonucleotide formyltransferase, and gamma-glutamyl hydro-