LY231514 (ALIMTA): Impact of Folic Acid and Vitamin B12 Supplementation on Safety

04 June 2001

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1. Introduction

1.1. Background Information

Consistent with the toxicity profile of other antifolates, studies of LY231514 (without the supplementation of folic acid and vitamin B12) identified myelosuppression as the principal dose-limiting toxicity, although nonhematologic toxicities of mucositis, diarrhea, vomiting and infection were also significant. The incidence of CTC Grade 3/4 neutropenia observed for LY231514 was approximately 50% [1], with the rate of possibly or probably drug-related death approximately 4%.

Given the relevance of folic acid to the pharmacology of antifolates, it is reasonable to postulate that functional folate status could be an important predictor of toxicity. Studies have suggested that plasma homocysteine is a much more sensitive measure of functional folate status than is serum folate or red blood cell folate [2, 3]. Methionine synthase is a highly folate-dependent enzyme that converts homocysteine to methionine. Thus, under conditions of folate deprivation, levels of plasma homocysteine increase. Elevated serum homocysteine can also result from vitamin B12 deficiency. The methylated form of vitamin B12 is a cofactor for methionine synthase. Under conditions of vitamin B12 deficiency, the homocysteine levels will increase because of inactiviation of the enzyme.

In 1998, a multivariate analysis was conducted to assess the relationship of vitamin deficiency markers, LY231514 exposure, and pre-specified baseline patient characteristics to toxicity following therapy with LY231514 [4]. Data were examined from 139 Phase 2 patients with tumors of the colon, breast, pancreas, and esophagus who had been treated with single agent LY231514 at 600 mg/m2 IV over 10 minutes once every 21 days. These patients had vitamin-deficiency markers of homocysteine (Hcys), cystathionine, and methylmalonic acid levels measured in plasma at baseline and once each cycle thereafter. Stepwise regression modeling, multivariate analysis of variance, and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity, and to predict which patients might be at high risk of experiencing such toxicity. Prognostic factors considered were age, gender, prior therapy, baseline albumin, liver enzymes, ANC, platelets, vitamin deficiency markers, and AUC.

In the analysis above, the B12 deficiency marker, methylmalonic acid, was highly correlated with homocysteine and was therefore removed from the initial multivariate analysis conducted in 1998 to eliminate issues of colinearity.

The initial analysis conducted in 1998 led to the following conclusions:

- The frequency of severe toxicities resulting from therapy with LY231514 is highly statistically linked with baseline plasma homocysteine levels and appears to be higher in patients with elevated pretherapy homocysteine levels.

- Elevated baseline homocysteine plasma concentrations (≥10 μM, for the 139 patients included in this analysis) highly correlate with the frequency of severe hematological (Grade 4 neutropenia and thrombocytopenia) and nonhematologic (Grade 3/4 mucositis, diarrhea, rash, or fatigue) toxicities following therapy with LY231514.
- Treatment with LY231514 had no effect over time on plasma concentrations of homocysteine.

Due in part to an increased incidence of drug-related deaths (8.3%; 3 of 36 patients) observed early in the Phase 3 pleural mesothelioma registration trial (JMCH), a second and more comprehensive multivariate analysis based on 880 patients without folic acid and vitamin B12 supplementation was performed in 1999 in order to determine which predictors might correlate with drug-related death (see pages 1-5 of LY231514 Annual Report submitted as Serial Number 194 to IND #40,061 on November 8, 1999; see also Appendix 1, LY231514 (MTA) Safety Analysis, 03 December 1999; submitted as Serial Number 195 to IND #40,061 on December 3, 1999). Because the decision to measure markers of folic acid and vitamins B6 and B12 metabolism in LY231514-treated patients was made during the Phase 2 development of the agent, these marker levels were available in only 11 of the 43 patients whose deaths were reported as possibly or probably related to LY231514. Stepwise regression modeling, multivariate analysis of variance, and discriminate analysis were implemented. Prognostic factors considered for LY231514-related deaths were age, gender, baseline serum albumin, liver enzymes (alkaline phosphatase, alanine transaminase, aspartate transaminase), ANC, platelets, AUC, pre-treatment weight, prior chemotherapy, tumor type, grade 4 neutropenia in conjunction with grade 3 or 4 infection (a surrogate indicator of febrile neutropenia), post baseline minimum platelet count, grade 3 or 4 diarrhea, and grade 3 or 4 mucositis.

This analysis led to the following conclusion:

- Grade 4 neutropenia accompanied by Grade 3/4 infection, Grade 3/4 diarrhea, and tumor type were all significantly associated with drug-related death.

A total of 305 of the 880 patients had baseline vitamin markers measured and recorded. To eliminate the complicating factors of the effect of folic acid supplementation on toxicity or, for Phase 1 studies, those LY231514 doses not being pursued, any patient who received folic acid supplementation at any point during therapy or who received any dosing regimen other than LY231514 500-600 mg/m^2 was removed from the analysis, leaving a final sample size of 246 patients. Data from this subset of patients were analyzed to determine which predictors might correlate with severe toxicity and to predict which patients are at high risk of experiencing such toxicity, especially those implicated in drug-related deaths. Stepwise regression modeling, multivariate analysis of variance, and discriminate analysis were implemented. Prognostic factors considered were age, gender, baseline serum albumin, liver enzymes (alkaline phosphatase, alanine transaminase, aspartate

transaminase), ANC, platelets, vitamin deficiency markers, pre-treatment weight, and AUC, tumor type, and prior treatment.

This analysis led to the following conclusions:

- Baseline homocysteine plasma concentration was a statistically significant predictor for febrile neutropenia, Grade 4 neutropenia, Grade 4 thrombocytopenia, and Grade 3 or 4 diarrhea.
- The results confirmed the findings of the original multivariate analysis that homocysteine plasma concentrations may be an important prognostic variable for predicting toxicity during LY231514 therapy.
- The data showed a trend of decreasing toxicity with decreasing baseline homocysteine level.
- The specific toxicities (Grade 4 neutropenia, febrile neutropenia, and Grade 3/4 diarrhea) associated with high-level baseline homocysteine were those toxicities associated with drug-related death.
- In contingency analyses designed to compare the rate of death in patients receiving a starting dose of 500 mg/m^2 versus 600 mg/m^2, it was found that there was no difference in the relationship between the incidence of drug-related deaths and starting dose.

1.2. Supplementation with Folic Acid and Vitamin B12

As a result of these analyses, it was postulated that reducing plasma homocysteine concentrations in patients given LY231514 would result in a reduction in the frequency of severe toxicity associated with this agent and consequently a reduction in deaths attributable to study drug. In addition, because the predictive nature of baseline homocysteine level behaved as a continuous risk factor for toxicity, the decision was made to supplement LY231514 study patients. Beginning in 2000, patients on all new and most on-going trials with LY231514 were supplemented with daily folic acid 350-1000 µg throughout the entire treatment and vitamin B12 1000 µg IM every 9 weeks and this was communicated to the FDA in communications to the FDA (Serial number 195 to IND #40,061 on December 3, 1999; 196 on December 10, 1999; 199 on December 21, 1999; 200 on December 22, 1999; 201 on December 22, 1999; 207 on February 16, 2000; and during a meeting between Lilly and the Division of Oncology Drug Products on March 1, 2000).

Most patients had a blood sample drawn for the measurement of baseline vitamin deficiency markers before supplementation began. A second blood sample for the purposes of measuring changes in vitamin deficiency markers following initial supplementation was drawn just prior to the first treatment with LY231514 and on a per cycle basis thereafter as long as the patient remained on study.

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