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MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity

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Introduction: MTA is a novel multitargeted antifolate with inhibitory activity against multiple enzymes. Phase I/II studies have shown activity in a variety of tumors. Historical data on other antifolates have suggested that a patient's nutritional status may play a role in the likelihood of experiencing severe toxicity. The purpose of this study was to assess the relationship of vitamin metabolites, drug exposure, and other prespecified baseline patient characteristics to toxicity following treatment with MTA.

Methods: Homocysteine (Hcys), cystathionine and methylmalonic acid were measured in 139 phase II patients with tumors of the colon, breast, pancreas, and esophagus 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 after one course of MTA. Prognostic factors considered were age, gen-

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der, prior treatment, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, and AUC.

Results: Statistically significant predictors of Grade 4 neutropenia (n=21 pts) were albumin ($p = 0.0006$) and Hcys ($p = 0.0012$), while Grade 4 thrombocytopenia (n=8) was highly predicted by Hcys ($p < 0.0001$) and pre-treatment AST ($p = 0.0012$). Hcys $\geq 10\mu M$ predicted Grade 4 neutropenia in cycle one 75% of the time. Grade 4 neutropenia was predicted by Hcys alone in 70% of cases. Hcys and albumin levels did not appear to change from baseline during treatment with MTA. While AUC was not found to be a predictor of toxicity, little variability was observed in AUC. Maximum values were still below AUC values related to hematologic toxicity in phase I studies.

Conclusions: Toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels ($\geq 10\mu M$) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA. Homocysteine was found to be better than albumin at predicting toxicity. These results apply to the tumor types studied. Further studies are underway in patients with renal impairment or patients who received prior cisplatin.

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