CÁNCER DE MAMA

A phase II trial of pemetrexed in advanced breast cancer: clinical response and association with molecular target expression.

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Abstract

PURPOSE: This phase II trial of pemetrexed explored potential correlations between treatment outcome (antitumor activity) and molecular target expression. EXPERIMENTAL DESIGN: Chemonaïve patients with advanced breast cancer received up to three cycles of pemetrexed 500 mg/m2 (10-minute i.v. infusion) on day 1 of a 21-day cycle, with folic acid and vitamin B12 supplementation. Tumors were surgically removed after the last cycle of pemetrexed as clinically indicated. Biopsies were taken at baseline, 24 hours after infusion in cycle 1, and after cycle 3. RESULTS: Sixty-one women (median age, 46 years; range, 32-72 years) were treated and were evaluable for response. Objective response rate was 31%. Simple logistic regression suggested a potential relationship between mRNA expression of thymidylate synthase (TS) and pemetrexed response (P = 0.103). Based on threshold analysis, patients with "low" baseline TS (< or = 71) were more likely to respond to pemetrexed than patients with "high" baseline TS (>71). Expression of baseline dihydrofolate reductase and glycinamide ribonucleotide formyl transferase tended to be higher in responders but this association was not significant (P > 0.311). TS expression increased significantly between baseline and biopsy 2 (P = 0.004) and dropped to near baseline levels at biopsy 3. Conversely, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase decreased after pemetrexed chemotherapy. CONCLUSIONS: Our results suggest a potential association between "low" pretreatment TS expression levels and response to pemetrexed chemotherapy. Future trials examining expression levels of other genes important to the folate pathway and/or breast cancer may identify a more robust multigene profile that can better predict response to this novel antifolate.