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LETTER TO THE EDITOR

Decrease in blood miR-296 predicts chemotherapy resistance and poor clinical outcome in patients receiving systemic chemotherapy for metastatic colon cancer

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Dear Editor:

MicroRNA (miRNA) is a new class of small, noncoding RNA that can regulate the expression of multiple genes. miRNAs have been implicated in a diverse number of cellular processes including cell proliferation, apoptosis, regulation of embryonic stem cell development, and cancer cell invasion. Recent studies have shown that, unlike other types of biomarkers, miRNAs in the circulation are remarkably stable making them robust and reliable biomarkers of cancer. We aim to investigate if specific miRNA(s) in the blood can provide a valuable noninvasive tool in predicting clinical outcome of patients enrolled in a phase II clinical trial of Sunitinib and Capecitabine in first-line treatment of metastatic colon cancer. Eight patients were enrolled in the trial and received Sunitinib 37.5 mg orally once daily and Capecitabine 1,000 mg orally twice daily. Serum samples were collected from patients prior to drug administration at baseline and then every 4 weeks. Serum miRNA analysis included 380 miRNAs. Change of miRNAs at 4 weeks compared to baseline (ratio less than 0.5 or larger than 1.5) was calculated and compared to patients' outcomes. The change in miR-296, one of the 380 miRNAs, demonstrated a statistically significant correlation with patients' clinical outcome and separated them into two groups.

Seven patients were included in the analysis. Three patients had decrease in the level of miR-296 at 4 weeks. Four patients had increase in the level of miR-296 during that time period. Compared to patients with longer survival and better clinical outcome, patients with shorter survival and poor clinical outcome exhibited a decrease in the level of miR-296 at 4 weeks compared to baseline (28 versus 0.43) (P=0.035). One patient (not included in the analysis) out of the eight treated had undetectable miRNA-296 levels prior to treatment and remained so at the end of the treatment. This patient had a poor clinical outcome.

Recent studies revealed a new function of miR-296 in cancer progression which is interesting and appears to be directly relevant to our results. In this report, miR-296 is progressively lost during tumor progression and correlates with metastatic disease in colorectal cancer. The patients with decrease in miR-296 at 4 weeks may reflect a more aggressive tumor phenotype with increased metastasis and tumor cell invasiveness. The loss of miR-296 may be one of the mechanisms for primary resistance of colorectal cancer to chemotherapy. Additionally, the implication of low serum miR-296 in cancer progression is also supported by the observation that one patient with a poor outcome (not included in the analysis) had undetectable serum miR-296 levels, prior to initiation of treatment and remained so at the end of the treatment. Taken together, our results indicate that the decrease in circulating miR-296 is associated with shorter survival and poor response to treatment with Sunitinib and Capecitabine. Further studies are needed to confirm these findings and evaluate its utility as a predictive and prognostic biomarker.

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