In Reply: The letter of Dr Altundag et al raises a few important questions for the interpretation of circulating DNA levels. With respect to human telomerase reverse transcriptase (hTERT) specificity, it was not our intention to use hTERT genomic amplification as a tumor-associated marker, but instead, we simply used it as a marker to quantify, by real-time polymerase chain reaction, the total amount of circulating DNA that includes not only tumor, but also normal DNA, possibly released in the circulation as a result of the tumor-host interaction. To our knowledge to date, the release of DNA into the bloodstream, measured by hTERT copy number, cannot be seen as a tumor-specific marker for lung cancer or any other tumor site. Nonetheless, we could measure with unprecedented accuracy the amount of plasma DNA in a large series of lung cancer patients and matched controls, and demonstrate a highly significant difference between these two groups.

On the other hand, a certain degree of cell-type specificity could be hypothesized since in our analysis (unpublished data), median hTERT DNA plasma levels in 60 patients with lung metastases from other cancers (15 ng/mL) or in 11 patients with inflammatory diseases (12 ng/mL) were lower than those detected in patients with non-small-cell lung cancer (NSCLC; 24 ng/mL).

We stated in the article that no association was observed between pathologic stage and plasma DNA at multivariate analysis. More specifically, median DNA levels were 25 ng/mL for stage 1A, 21 ng/mL for stage 1B, 35 ng/mL for stage 2, and 23 ng/mL for stage 3 (Kruskall-Wallis test \( P = .30 \)). This observation is consistent with our prior reports of a high frequency of microsatellite alterations, \( p16^{INRA} \) hypermethylation, and \( p53 \) mutations in plasma DNA of early-stage NSCLC.

Having tested the entire cohort of 1,035 high-risk individuals enrolled onto our pilot trial, we will assess in the near future if very small computed tomography (CT)–detected lung cancers (< 1 cm) show a level of DNA release into plasma similar to the one observed in symptomatic patients with NSCLC, thus demonstrating the real contribution of this polymerase chain reaction assay to early lung cancer detection.

It is certainly correct to underline that some overlapping occurred in the distribution of plasma DNA between cases and controls, which is also evident in the confidence limits of Table 2 of the article. Choosing a low DNA cutoff to designate a person as “positive” would increase diagnostic sensitivity at the expense of false-positives and poorer specificity. On the contrary, selecting a high DNA cutoff would then maximize the specificity at the expense of sensitivity, increasing the number of false-negatives. As a matter of fact, it is unlikely that a single tumor marker could perfectly discriminate lung cancer patients from individuals without disease. The ultimate value of plasma DNA quantification may not be to replace spiral CT as a primary tool for early lung cancer detection, but instead to improve the interpretation of suspicious CT or positron-emission tomography images or to decide how often to repeat spiral CT based on individually tailored risk.

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The authors indicated no potential conflicts of interest.

REFERENCES


Oxaliplatin Toxicity Masquerading As Recurrent Colon Cancer

To the Editor: A 69-year-old white male, while receiving bicalutamide, leuprolide acetate, and finasteride for locally recurrent prostate cancer was diagnosed with moderately differentiated adenocarcinoma of the rectum, Dukes’ stage C. He underwent anterior abdominoperineal resection and received 45 Gy in 25 fractions to the pelvis. While receiving radiation therapy he was given 500 mg/m²/d of capecitabine for 14 of 21 days. After radiation therapy, the patient was given capcitabine 1,000 mg/m²/d divided in two doses for 14 of 21 days, plus oxaliplatin 130 mg/m² intravenously on day 1 every 21 days for a total of four 21-day courses. Shortly after the fourth course, the patient presented with abdominal distension and severe ascites. The ascitic fluid was a sterile transudate devoid of tumor cells. Prostate specific antigen, prostatic acid phosphatase, carcinoembryonic antigen, CA-19-9, AST, ALT, alkaline phosphatase (AP), lactate dehydrogenase, and

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REFERENCE


gamma glutamyl transferase (GGT) were all within normal limits. Serum albumin was 3.3 g/dL (range, 3.8 to 5 g/dL). Renal function was normal.

An exhaustive work-up for metastatic cancer included computed tomography imaging of the chest, abdomen, and pelvis and diagnostic laparoscopy. All studies revealed absence of recurrent cancer. On laparoscopy, the liver appeared grossly normal and no tumor was noted. Computed tomography imaging through the liver revealed a 5 cm hemangioma confirmed by magnetic resonance imaging, which on biopsy confirmed that diagnosis. Hepatic color flow Doppler evaluation of the hepatic and portal veins demonstrated that the portal vein was patent with hepatopetal flow, and a hepatic vein was identified which was patent with blood flowing toward the inferior vena cava and heart.

An echocardiogram ruled out right heart failure and there was absence of pericardial effusion. Inferior venacavogram and hepatic venograms with pressure measurements revealed that the right and middle hepatic veins were devoid of stenosis, thrombosis, or web formation. The wedge hepatic vein pressure, a reflection of the portal vein pressure, was elevated to 18 to 20 mmHg, confirming portal hypertension. Transjugular liver biopsy revealed severe hepatic sinusoidal obstruction with central vein fibrosis and no evidence of cirrhosis (Figs 1 and 2). The sinusoidal lesions were morphologically identical to those described by Rubbia-Brandt. A transjugular intrahepatic portal-systemic shunt was placed. The ascitic accumulation decreased.

The patient’s course in hospital was complicated by elevation of AP, GGT, and total bilirubin to four times the upper limit of normal (starting 4 weeks after hospitalization) while the AST and ALT remained within the normal range. The patient became encephalopathic, developed renal failure requiring dialysis, upper gastrointestinal bleed due to gastritis, atrial fibrillation, and bilateral bacterial pneumonia. He was unable to be weaned from a respirator and he died after a 7-week hospitalization.

Our original pathologic review of the patient’s liver biopsy revealed a histologic pattern similar to that described in the Budd-Chiari syndrome, or in children receiving radiation to the liver, or in those receiving high-dose chemotherapy with autotransplant. The hepatic Doppler and hepatic venogram studies confirmed the absence of vascular obstruction as found in the Budd-Chiari syndrome. The patient received no hepatic radiation and usual dose capecitabine and oxaliplatin.

Serendipitously, a recent publication by Rubbia-Brandt et al described liver pathology in their patients undergoing neoadjuvant chemotherapy. Perisinusoidal fibrosis, severe sinusoidal obstruction, and fibrotic venular occlusion, as noted in our patient, was noted in liver biopsy specimens in 44 (51%) of 87 of their hepatectomies performed after neoadjuvant chemotherapy, and in 34 (79%) of 43 colorectal cancer patients receiving oxaliplatin. In some patients, these lesions were found to progress in the absence of continued chemotherapy. They gave no instances of clinical abnormality caused by such lesions in their patient population. They found a significant correlation between the presence of liver lesions and the use of oxaliplatin: 34 (79%) of the 43 patients treated with oxaliplatin developed lesions, as opposed to 10 (23%) of the 44 who did not (P < .001). The amount of oxaliplatin received was quantified as a cumulative dose expressed in mg/m² and ranged from 280 to 1,600 mg/m². Our patient received a total dose of 520 mg/m².

This case is important, because to our knowledge, it is the first clinical report of portal hypertension and ascites likely due to oxaliplatin hepatic toxicity. Toxicity occurred in a patient who did not have hepatic metastases, whose
liver had never been subjected to surgical intervention, and within the context of adjuvant chemotherapy. The patient had no signs of nephrosis, right heart failure, pericarditis, peritonitis, Budd-Chiari syndrome, hepatitis, alcohol abuse, or cirrhosis, and at the time of presentation with clinical ascites the AST, ALT, AP, GGT, total bilirubin, and lactate dehydrogenase were normal.

A search of the medical literature for similar clinical toxicity revealed a solitary case of clinical hepatotoxicity leading to death reported in a patient receiving raltitrexed plus oxaliplatin.² Details of this case were not given.

The presentation of ascites in a patient receiving chemotherapy for colorectal cancer is often construed as recurrent cancer. In such cases when oxaliplatin has been administered we recommend an aggressive search for recurrent or progressive cancer with a low threshold for liver biopsy in an attempt to recover noncancerous tissue. The presence of portal hypertension should be investigated. The true frequency of clinically important oxaliplatin hepatic toxicity is unknown; however, histopathologic evidence for such toxicity was reported in 79% of patients.¹ Physicians should be aware that oxaliplatin hepatic toxicity might confuse the clinical evaluation of patients receiving the drug by masquerading as progression of cancer. Since the pathologic changes may progress for several months after withdrawal of chemotherapy, it is possible that clinical signs of hepatic dysfunction may occur many months or possibly years after therapy.

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REFERENCES

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