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Medullary Thyroid Cancer and Pseudocirrhosis: Case Report and Literature Review

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KEY WORDS
Medullary thyroid cancer, pseudocirrhosis, carcinomatous cirrhosis

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E-JOURNAL LINKED ABSTRACT

Pseudocirrhosis is a rare form of liver disease that causes clinical symptoms and shows radiographic signs of cirrhosis, but that has histologic features suggesting a distinct pathologic process. In the setting of cancer, hepatic metastases and systemic chemotherapy are suspected causes of pseudocirrhosis.

We present the case of a 49-year-old woman with medullary thyroid carcinoma metastatic to the liver who developed pseudocirrhosis. The patient was initially enrolled in a phase I clinical trial of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in combination with sunitinib (NCT00599924). After this patient's liver metastases regressed measurably, she was switched to sunitinib maintenance. After 4 months of combination therapy with FOLFOX–sunitinib and 15 months of sunitinib maintenance, she developed abdominal bloating, early satiety, and right upper quadrant pain that increased with inspiration.

Computed tomography of the abdomen revealed cirrhotic morphology changes in the liver, including the appearance of a nodular surface and capsular retraction. The patient had no risk factors for cirrhosis and laboratory testing for causes of liver disease were normal or negative. Core-needle liver biopsy demonstrated sheets and nests of epithelioid and spindle cells resembling the primary tumor; septal fibrosis and regenerative nodules typical of cirrhosis were not observed. The background hepatic plate architecture was intact. Laboratory studies showed increased aminotransferases, alkaline phosphatase, and international normalized ratio, and decreased albumin.

Portal hypertension, esophageal varices, portal hypertensive gastropathy, and hepatic hydrothorax developed as a result of advanced liver disease. Because of disease progression, sunitinib was discontinued, and the patient was managed with sorafenib.

Pseudocirrhosis has often been attributed to chemotherapeutic agents, particularly in the context of metastatic breast cancer. The toxicity profiles of FOLFOX and sunitinib include hepatic steatosis and other forms of hepatotoxicity, but cirrhotic-like disease has not been reported. Considering the transformation of discrete hepatic metastases into a diffuse carcinomatous infiltrate and the unrelated toxicities of FOLFOX and sunitinib, we diagnosed this patient with carcinomatous pseudocirrhosis secondary to metastatic medullary thyroid carcinoma. We discuss the diagnosis of pseudocirrhosis in this case and review the literature regarding pseudocirrhosis in cancer.

Phase I Study of the Plk1 Inhibitor BI 2536 Administered Intravenously on Three Consecutive Days in Advanced Solid Tumours

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KEY WORDS
Polo-like kinase, Plk1 inhibitor, BI 2536, phase I, dose escalation, solid tumours

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Background: BI 2536 is a potent and highly selective inhibitor of serine-threonine polo-like kinase 1 (Plk1), a key regulator of cell cycle progression. This two-part, first-in-humans study was conducted to determine the maximum tolerated dose (MTD) and safety profile of BI 2536 in two schedules in patients with advanced solid tumours.

*With the increasing national and international popularity and exposure of *Current Oncology*, the queue of excellent submissions continues to lengthen. After substantial consideration, the journal's management has determined that the best way to manage this abundance is to move to a "hybrid" of combined print and electronic publication, with every e-manuscript being supported by a full print abstract and key words, and of course, indexing in PubMed for international recognition.

In the first part of the study, the MTD of BI 2536 was determined to be 200 mg when administered as a 60-minute intravenous infusion on day 1 of each 3-week treatment cycle. Here, we report the findings of the second part, in which BI 2536 was investigated as a 60-minute infusion on days 1–3 every 3 weeks.

Methods: Patients with advanced solid tumours received a single 60-minute intravenous infusion of BI 2536 (50–70 mg) on days 1–3 of each 21-day treatment course. Those without disease progression or untenable toxicity could receive additional treatment courses. The primary endpoint of MTD was determined based on dose-limiting toxicities (DLTS) in the first treatment cycle; secondary endpoints included safety, pharmacokinetic profile, and antitumour activity according to Response Evaluation Criteria in Solid Tumors.

Results: A total of 21 patients were entered into the study. Of 7 patients treated with the initial 50-mg dose of BI 2536, 1 experienced a DLT (grade 3 increase in alanine aminotransferase). Both patients receiving the next higher dose of BI 2536 (70 mg), experienced DLTS during the first treatment course (grade 4 thrombocytopenia and grade 4 neutropenic fever in one patient; and grade 3 hematochezia, grade 4 thrombocytopenia, grade 4 anemia, and grade 3 enterocolitis in the other). Among the 6 patients subsequently treated at the 60-mg intermediate dose of BI 2536, none experienced a DLT during the first treatment course. Thus, the MTD for BI 2536 was determined to be 60 mg for the investigated dosing schedule. An additional 6 patients were then treated at the MTD, with 1 patient experiencing a DLT in the first cycle (grade 3 fatigue).

Across all dosing cohorts, 8 patients (38%) experienced stable disease, including 4 of 12 (33%) patients treated at BI 2536 60 mg; no objective responses were observed. The most frequently reported drug-related adverse events were mild-to-moderate fatigue (62%), leukopenia (38%), alopecia (33%), constipation (29%), nausea (29%), mucosal inflammation (29%), anorexia (29%), and neutropenia (29%). The most common grade 3 or 4 drug-related adverse events were leukopenia (38%) and neutropenia (29%). The pharmacokinetics of BI 2536 were linear within the dose range tested. Plasma concentration profiles exhibited multi-compartmental pharmacokinetic behaviour, with a terminal elimination half-life of 20–30 hours.

Conclusions: BI 2536 showed an acceptable safety profile in this study, warranting further investigation of Plk1 inhibitors in this patient population.

Fine-Needle Aspiration Biopsy Versus Core-Needle Biopsy in Diagnosing Lung Cancer: A Systematic Review

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KEY WORDS
Fine-needle aspiration biopsy, core-needle biopsy, diagnostic characteristics, diagnostic yields, lung cancer, systematic review

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Background: Globally, lung cancer is the leading cause of cancer-related mortality, and an early but specific diagnosis is important for the optimal treatment of lung cancer patients. The objective of this systematic review was to compare the diagnostic characteristics of fine-needle aspiration biopsy (FNAB) and core-needle biopsy (CNB) as used during the investigation of lung lesions in lung cancer patients.

Methods: The MEDLINE and EMBASE databases (from January 1, 1990, to September 14, 2009), the Cochrane Library (to Issue 4, 2009), and some well-known guideline Web sites (such as the U.S. National Guideline Clearinghouse, the U.K. National Institute for Health and Clinical Excellence, the Scottish Intercollegiate Guidelines Network, and the American Society of Clinical Oncology guidelines, among others) were searched for relevant articles. Randomized trials or comparative cohort studies were included if they reported diagnostic characteristics, diagnostic yields, or complication rates; studies were excluded if the biopsy results from either FNAB or CNB were regarded as a part of the reference standard or if the FNAB and CNB had been performed on different patient populations.

Results: No systematic reviews or practice guidelines focusing on a comparison of FNAB and CNB for diagnosing lung malignancies were available in the literature. The electronic search identified one hundred twenty-two citations. Ten articles met the study selection criteria. One additional article that

did not state the reference standard was analyzed separately from other eligible studies. Thus, eleven studies were included in the systematic review. For the overall diagnostic characteristics of FNAB and CNB (differentiating malignant from benign lesions without specific cytologic or histologic subtype diagnosis), the ranges of sensitivity were, respectively, 81.3%–90.8% and 85.7%–97.4%; of specificity, 75.4%–100.0% and 88.6%–100.0%; and of accuracy, 79.7%–91.8% and 89.0%–96.9%. For the specific diagnostic characteristics of FNAB and CNB (identifying the histologic subtype of a malignancy or the specific benign diagnosis), the ranges of sensitivity were, respectively, 56.3%–86.5% and 56.5%–88.7%; of specificity, 6.7%–57.1% and 52.4%–100.0%; and of accuracy, 40.4%–81.2% and 66.7%–93.2%. The complication rates for pneumothorax and hemoptysis were not higher with CNB than with FNAB. No study has compared the diagnostic yields of FNAB and CNB for molecular predictive or prognostic-markers.

Discussion and Conclusions: To date, evidence addressing the differences between FNAB and CNB in the identification of lung malignancies remains elusive. However, in the diagnosis of specific benign lesions, specificity is likely higher with CNB than with FNAB. Well-designed and good-quality studies to compare FNAB with CNB for diagnostic characteristics and yields in diagnosing lung cancer are desirable.

Role of Pemetrexed in Advanced Non-Small-Cell Lung Cancer: Meta-Analysis of Randomized Controlled Trials, with Histology Subgroup Analysis

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KEY WORDS
NSCLC, meta-analysis, pemetrexed

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Purpose: Platinum-based regimens represent the standard first-line treatment for non-small-cell lung cancer (NSCLC). However, the role that other emerging chemotherapy agents such as pemetrexed play is unclear. It is unknown whether histology represents a determining factor in the selection of treatment.

Methods: We performed a systematic review of the literature for randomized controlled trials that compared the efficacy of pemetrexed with that of other treatments or with placebo in advanced NSCLC. Data and quality assessment were done using the Grading of Recommendations Assessment, Development and Evaluation Working Group guidelines. Data on histologic subtypes were obtained whenever reported or by contacting the primary authors of the relevant studies. The main outcome was overall survival at 12 months; secondary outcomes included differences between squamous and non-squamous histology and between first- and second-line use of pemetrexed.

Results: Five trials comparing pemetrexed with other treatments or with placebo were identified. A total of 3541 patients were included in the pooled analysis of hazard ratios (HRS) that was used to estimate overall effect. Compared with other treatments, pemetrexed resulted in superior overall survival for patients treated with that agent [HR: 0.89; 95% confidence interval (CI): 0.80 to 0.99]. The survival benefit appeared to be limited to patients with non-squamous histology (HR: 0.82; 95% CI: 0.73 to 0.91). Pemetrexed was inferior to other chemotherapy options in patients with squamous histology (HR: 1.19; 95% CI: 0.99 to 1.43). No difference in overall survival was observed for pemetrexed in the first line compared with the second line (HR: 0.89 vs. 0.88), and no significant heterogeneity was observed between the trials in the analysis. The side-effect profile favoured pemetrexed, with less neutropenia observed.

Conclusions: Pemetrexed appears to be more effective than other chemotherapy agents in the treatment of NSCLC. The benefit appears to be limited to patients with non-squamous histology. That finding is consistent with differential expression of thymidylate synthase, pemetrexed's target enzyme, in different lung cancer subtypes, and it will have implications concerning the need to further subclassify lung cancer patients, affecting the methods used to obtain the tissue and process it for histology reporting.

Increased Alpha-Fetoprotein Receptor in the Serum of Patients with Early-Stage Breast Cancer

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KEY WORDS
Alpha-fetoprotein, AFP, AFP receptor, RECAF, serum, tumour marker, biomarker, oncofetal antigen, sensitivity,

specificity, radioimmunoassay, serum test, early-stage, breast cancer

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The receptor for alpha-fetoprotein (RECAF) is an oncofetal antigen found in most types of cancer. Using a competitive radioimmunoassay, we measured the concentration of serum RECAF in three sets of samples.

Set 1 was blind and consisted of 119 normal control subjects, 43 breast cancer patients in stages I and II, and 20 patients with benign breast conditions. In that set, the assay discriminated normal from cancer samples with a receiver operating characteristic for the area under the curve (ROC_{AUC}) of 0.983 and a 95% specificity with 93% sensitivity at a cut-off of 4.6 K (arbitrary) RECAF units. At a cut-off of 7.3 K units, the sensitivity was 72% with 100% specificity when comparing samples from cancer patients and normal subjects. At the same cut-off value, the specificity was 85% with 72% sensitivity when cancer patients were compared with patients having benign lesions of the breast. On the same samples, carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) respectively showed 39% and 41% sensitivity, with 95% specificity, for control samples compared with cancer samples, and sensitivities of 34% and 44%, with 85% specificity, for benign breast lesion samples compared with cancer samples.

Set 2 consisted of 353 control, 30 benign, and 64 cancer samples at stages II and III. The sensitivity of the RECAF assay to discriminate normal from cancer samples was 97%, with 97% specificity. For benign samples compared with cancer samples, sensitivity was 87%, with 97% specificity. Set 3 included only 40 control and 40 cancer samples. The sensitivity for that set was 89%, with 100% specificity. Sets 2 and 3 were not tested with CEA or CA15-3.

Our results strongly suggest that the RECAF assay could be used for detecting breast cancer in its early stages.