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## INSIDE



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# Detection and Significance of Circulating Tumor Cells in Patients with Metastatic Breast Cancer

ABSTRACT & COMMENTARY

***By William B. Ershler, MD***

***Synopsis:*** *In this review of 195 patients with metastatic breast cancer, detection of 5 or more circulating cancer cells in 7.5 mL of whole blood correlated with reduced overall survival. Furthermore, the presence of extensive bone metastases, as detected by PET/CT, was shown to be associated with increased circulating tumor cells (CTC).*

**Source:** De Giorgi U, et al. Circulating tumor cells and bone metastases as detected by FDG-PET/CT in patients with metastatic breast cancer. *Ann Oncology*. 2010;21:33-39.

Several studies have suggested a prognostic and predictive role for circulating and disseminated tumor cells in patients with breast cancer. It has been postulated that the circulating tumor cell (CTC) number will become a useful tumor marker, valuable both in prognosis, as well as measurement of effective treatment.[1,2] However, implementation of this assay into clinical routine has been cumbersome. CTCs are infrequent enough that they are recognized only by using a combination of surface and intracellular markers and, just recently, a number of technical advances have made their reliable detection possible. It has become apparent that, unlike other tumor markers, the number of CTCs does not necessarily correlate with the total tumor burden.[3,4] For example, in one recent study, there was only limited correlation between CTC levels and radiographic measurement of tumor load.[5]

PET (2-[fluorine-18]fluoro-2-deoxy-D-glucose-positron emission tomography) is more sensitive than conventional imaging in the detection of breast cancer metastases and, together with computerized tomography (CT), there is greater anatomical precision with regard to metastatic disease.[6,7] Thus, if there is any correlation between CTC and the extent or distribution of metastatic disease, it would seem logical that this might be best determined by PET/CT

rather than other imaging techniques. Accordingly, De Georgi et al at M.D. Anderson in Houston evaluated the relationship between the detection and prognostic significance of CTCs and sites of metastases detected by PET/CT in patients with metastatic breast cancer (MBC). Between May 2004 and January 2008, 195 patients with relapsed/progressive MBC underwent whole-body FDG-PET/CT and provided blood samples for assessment of CTC count.

Higher CTC numbers were detected in patients with bone metastases relative to those with no bone lesions (mean 65.7 vs. 3.3, $p = 0.0122$) and in patients with multiple bone metastases relative to those with one or two bone lesions (mean 77.7 vs. 2.6, $p < 0.001$). CTCs predicted overall survival (OS) in 108 patients with multiple sites of metastases, including bone ($p = 0.0008$), but not in 58 without bone metastases ($p = 0.4111$) and in 29 with bone involvement only ($p = 0.3552$). Of 16 patients with human epidermal growth factor receptor 2 (HER-2)-positive tumors who were treated with trastuzumab-based regimens, 15 patients had < 5 CTCs at progression. In multivariate analysis, CTCs, not bone metastases, remained a significant predictor of OS.

## ■ COMMENTARY

In this retrospective analysis of 195 patients with metastatic breast cancer, the presence of extensive bone involvement, as detected by PET/CT, was shown to be associated with increased CTC numbers. The study clearly indicated a difference in frequency and number of CTC in those with bone metastases compared to those with metastatic disease at other sites. Even though it is curious that those with bone metastases alone (i.e., without metastases at other sites) did not have significantly more CTC than those without bone metastases, it is clear that patients with extensive bone metastases were most likely to have high CTC numbers and, in fact, poorest overall survival.

It is notable that 15 of 16 patients with HER2-positive tumors, who were treated with trastuzumab-based regimens, had < 5 CTCs at the time of progression, suggesting that trastuzumab might be affecting tumor-cell circulation. This finding may have important biological implications, and warrants prompt confirmation.

Clinical oncologists are becoming aware of the importance of detecting CTC in patients with breast cancer. In addition to providing insights into the biology of breast cancer metastases, it is now clear that CTC numbers provide significant, independent prognostic information. This report provides evidence for a strong correlation of CTC and extensive bone involvement. Yet, how this information becomes applied to the management of breast cancer, in the adjuvant or metastatic setting, remains in the realm of clinical investigation. ■

## References


1. Amadori A, et al. Circulating and disseminated tumor cells in the clinical management of breast cancer patients: Unanswered questions. *Oncology*. 2009;76: 375-386.
2. Mostert B, et al. Circulating tumor cells (CTCs): Detection methods and their clinical relevance in breast cancer. *Cancer Treat Rev*. 2009;35:463-474.
3. Gaforio JJ, et al. Detection of breast cancer cells in the peripheral blood is positively correlated with estrogen-receptor status and predicts for poor prognosis. *Int J Cancer*. 2003;107:984-990.
4. Cristofanilli M, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med*. 2004;351:781-791.
5. Budd GT, et al. Circulating tumor cells versus imaging — predicting overall survival in metastatic breast cancer. *Clin Cancer Res*. 2006;12:6403-6409.
6. Hodgson NC, Gulenchyn KY. Is there a role for positron emission tomography in breast cancer staging? *J Clin Oncol*. 2008;26:712-720.
7. Cohade C, Wahl RL. Applications of positron emission tomography/computed tomography image fusion in clinical positron emission tomography-clinical use, interpretation methods, diagnostic improvements. *Semin Nucl Med*. 2003;33:228-237.



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# *Illustrative Case Series*

*Beginning with this month's issue, we will spotlight a new case series that involves a guest oncologist reviewing a pertinent case study in the field. In upcoming issues, we will be adding a new round-up section featuring an expert in a particular specialty of oncology, as well as a fresh new look for the publication.*

# Colon Cancer in a Piano Instructor

CASE STUDY

***Guest Discussant, Robert Fenton, MD, PhD***
*Associate, Institute for Advanced Studies in Aging, Washington, DC*

*Dr. Fenton reports no financial relationship relevant to this field of study.*

## Case History

A 68-YEAR-OLD WHITE FEMALE PRESENTED TO HER internist complaining of fatigue for the past month. The patient is a piano teacher who traveled to her students' houses for their lessons, which had become a significant effort for her. She complained of no other symptoms, specifically no abdominal pain or change in appetite, weight, or bowel habits, as well as no chest pain, dyspnea, orthopnea, or edema. She denied noticing blood in her urine or stool, and had no vaginal bleeding. Her past medical history was notable for hypertension, osteoarthritis of both knees, and osteoporosis. She has two grown, healthy children, never smoked, and occasionally drank a glass of wine with dinner. She received yearly mammograms, Pap smears, and had her last colonoscopy seven years earlier (no abnormalities were found). Her chronic medications were hydrochlorothiazide, lisinopril, calcium, vitamin D, and Fosamax. In addition, she took Motrin 400 mg whenever her arthritis was bothering her, as often as 3-4 times per day. Her blood pressure was 125/74, heart rate 85, and room air oxygen saturation 94%. There were no orthostatic changes. Her physical exam was unremarkable other than mild pain on range-of-motion testing of both knees. Laboratory studies revealed a microcytic anemia (MCV 79) with a hemoglobin of 10.4 g/dL and a hematocrit of 32%. WBC was 6,300, with a normal differential, and there were 235,000 platelets. SGOT, SGPT, bilirubin, LDH, electrolytes, and renal function were all within normal limits. Routine blood tests performed four years earlier revealed a hemoglobin of 13.9 g/dL and a hematocrit of 42%.

## Differential Diagnosis

The patient has a microcytic anemia with fairly acute onset of exertional dyspnea, especially for someone with no history of smoking, pulmonary, or cardiac disease. Therefore, her exertional dyspnea is probably related to the anemia. Iron deficiency is almost certainly the cause of the anemia, but what is the cause of the iron deficiency? Given the history of significant NSAID use, gastric ulcer with chronic bleeding must be ruled out. Other possibilities would include other sources of bleeding, none of which are apparent from the history. This does not, however, eliminate the possibility of a bleeding source anywhere in the GI tract, and the possibility of colorectal cancer cannot be ignored.

## Work-up

Blood tests confirmed the diagnosis of iron deficiency: serum iron, 60 mcg/dL; serum ferritin, 14 ng/mL; TIBC, 380 mcg/dL; transferrin saturation, 11%. Ferrous sulfate 325 mg po/tid to be taken with ascorbic acid tablets (250 mg) was prescribed. An EKG was normal.

## Standard of Care

The patient was referred to a gastroenterologist, who performed an upper endoscopy that demonstrated some mild gastritis, but no ulcers or obvious source of bleeding. Prilosec was prescribed, and a colonoscopy was scheduled for the following week. This demonstrated a large, fungating lesion in the cecum, measuring approximately 6 cm in diameter. Biopsy of the mass showed moderately differentiated adenocarcinoma. CT scan of the abdomen and pelvis performed with contrast showed mild thickening of the wall of the bowel in the region of the cecum, but no evidence of perforation, hepatic metastases, or enlarged LN. CXR was normal, and CEA was 8.5 ng/mL. The patient was taken to surgery, where the cecal mass was identified and a right hemicolectomy with anastomosis was performed; no perforation or tumor penetration of the bowel wall was noted. Pathology revealed a 5.5 cm, moderately well-differentiated adenocarcinoma with penetration into the muscularis mucosa (T2). The surgical specimen contained 23 LN, five of which were positive for adenocarcinoma. Surgical margins were adequate (> 5 cm) and free of tumor. The patient made an unremarkable recovery and was referred to a medical oncologist for adjuvant chemotherapy for stage III colon cancer.

## Considerations for Adjuvant Therapy in Colon Cancer

The benefit of adjuvant chemotherapy for stage III colon cancer was established by the NSABP C-03 and NCCTG phase-III, randomized studies. In both trials, 5-FU plus leucovorin was administered according to the Mayo Clinic bolus schedule (5-FU, 425 mg/m$^2$ d1-5 every 4-5 weeks) for six cycles.[1,2] These data were confirmed by the IMPACT study of pooled data from three randomized studies of Dukes B or C patients who received 5-FU/LV or observation; a three-year OS benefit of 83% vs. 78% was noted (22% reduction in death).[3]

A subsequent study showed that infusion of 5-FU-LV by the de Gramont regimen (LV 200 mg/m$^2$ over 2h followed by 5-FU 400 mg/m$^2$ bolus and 600 mg/m$^2$ continuous IV infusion over 22 hours, repeated on day two and every two weeks) was at least as effective as bolus 5-FU/LV, but caused less diarrhea, mucositis, and neutropenia.[4] Note that a statistically significant benefit of adjuvant therapy for DFS and OS has only been observed in patients with positive LN (stage III, Dukes C). The role of adjuvant therapy for LN-negative disease (stage II, Dukes B) is generally not recommended, except in patients with high-risk features (e.g., T4 primary, perforation or obstruction, fewer than 13 LN identified in surgical specimen, lymphovascular, or neuronal microscopic invasion in primary tumor).

More recently, capecitabine, an oral fluoropyrimidine, was shown to be at least as effective as 5-FU/LV, and was FDA approved for the adjuvant therapy of stage III colon cancer.[5] It is well tolerated when administered at 1 g/m$^2$ BID for 14 of 21 days, with hand-foot syndrome being increased compared with 5-FU/LV regimens. Capecitabine is costly and not covered by all insurance companies for adjuvant treatment of colorectal cancer.

The MOSAIC trial demonstrated a significant improvement when oxaliplatin was added to 5-FU/LV in the adjuvant setting. In this randomized study of 2,246 patients with resected stage-II or -III colon cancer, patients received either the standard de Gramont infusional 5-FU/LV course of therapy, with or without the addition of oxaliplatin (85 mg/m$^2$), in a regimen designated FOLFOX4.[6] With a median follow-up of over 6.5 years, FOLFOX resulted in a significant improvement in DFS (73 vs. 67%, HR 0.80) and OS (79 vs. 76%, $p$ = 0.046).[7] The benefits were noted in stage III, but not stage II patients. Grade 3 peripheral neuropathy was noted in 13% of FOLFOX patients, but < 1% had persistent grade 3 neuropathy after four years. NSABP C-07 randomized patients to weekly 5-FU/LV (Roswell Park regimen), with or without oxaliplatin, every other week (treatment on a six- out of eight-week cycle).[8] Addition of oxaliplatin significantly improved DFS, with a trend toward improved OS, again only in stage-III patients. This regimen, using bolus 5-FU, appeared to be significantly more toxic than FOLFOX4 (e.g., diarrhea and dehydration). In another phase-III study, the addition of oxaliplatin (130 mg/m$^2$ dL, every 21 days) to capecitabine (1 g/m$^2$ BID for 14 of 21 days) (referred to as the Xelox regimen) was shown to have a reasonable toxicity profile when compared to either the Mayo clinic or Roswell Park bolus 5-FU/LV adjuvant regimens, with more peripheral neuropathy and hand-foot syndrome.[9] Efficacy data have not been published yet. On the basis of these and other studies, the addition of oxaliplatin to fluoropyrimidines is now the established standard of care for the adjuvant therapy of stage-III colorectal cancer.

Amazingly, a number of phase-III studies have demonstrated that irinotecan, a topoisomerase I inhibitor that is an important component of the treatment of metastatic colon cancer, provides no additional benefit to bolus or infusional 5-FU/LV in the adjuvant setting;[10,11] the reason for this is not apparent. Similarly, although the addition of bevacizumab (Avastin) to FOLFOX and other regimens significantly enhances anti-tumor activity against metastatic disease, a recent phase-III study demonstrated the bevacizumab + FOLFOX6 was not better than FOLFOX6 alone in the adjuvant setting.[12]

## Considerations for Adjuvant Therapy in Elderly Patients

Adjuvant chemotherapy for stage-III colorectal cancer provides an approximate 30% decreased risk of recurrence and a 22%-32% reduction in mortality. The relative benefit of adjuvant 5-FU/LV and capecitabine is just as great in older patients as in younger patients.[13] Furthermore, the toxicity profiles are similar, with a trend toward more diarrhea in elderly patients receiving the Mayo bolus regimen.[14] The data for FOLFOX treatment in patients > 70 years are ambiguous, with one pooled analysis demonstrating an equal benefit to younger patients and one indicating that the benefits did not extend to patients older than age 70.[15,16] These data suggest that it is important to consider the overall condition of elderly patients before recommending oxaliplatin-based regimens that have greater treatment-related toxicities than 5-FU/LV alone. Fit elderly patients may receive mFOLFOX6, but careful consideration must be given to less fit or frail elderly patients. For patients who cannot receive oxaliplatin (pre-existing neuropathy or medical co-morbidities), 5-FU/LV (de Gramont regimen preferable due to reduced toxicity) or capecitabine for six months is a reasonable choice.

## How to Treat this Patient?

This patient may very well benefit from adjuvant therapy. By six weeks postoperatively, her CEA had decreased to 2.2 ng/m and her Hb increased to 13.5 g/dL, coincident with recovery of her exercise tolerance. Given her excellent performance status, she was a candidate for six months mFOLFOX6. However, the patient expressed concerns that oxaliplatin-induced neuropathy could end her piano-playing career. Long-term morbidity from oxaliplatin-based regimens is due to distal sensory neuropathy that can be expected to be grade 3 in 10%-15% of patients receiving 85mg/m$^2$ on an every-other-week schedule for more than four months. In most cases, this neuropathy will resolve, but this occurs over months to years.[7] The options available for this patient include: 1) not using oxaliplatin and treating with six months of 5-FU/LV on the de Gramont schedule; 2) treating with six months of mFOLFOX6, with careful monitoring for the development of neuropathy. The problem with this approach is that neuropathy can develop insidiously and progress even after the oxaliplatin is stopped. Although recent data suggest that infusions of 1 g of calcium gluconate and magnesium sulfate, pre- and post-oxaliplatin, can ameliorate neuropathy, the physician cannot guarantee that significant neuropathy will not occur;[17,18] 3) since neuropathy appears to occur after four months of FOLFOX therapy (using 85 mg/m$^2$ of oxaliplatin), it would be reasonable to treat the patient with 3-4 months of mFOLFOX6 with calcium/magnesium infusions, and then complete the six months with 5-FU/LV alone. Ultimately, the patient will need to weigh the risks/benefits, as presented by her oncologist, and then decide whether to receive oxaliplatin-based adjuvant treatment.

## Areas Requiring Further Research

1. Is six months of adjuvant therapy really needed, or would 3-4 months be as efficacious?
2. Are there pharmacogenomic indicators that can identify patients who are most susceptible to toxic effects of drugs (e.g., neuropathy from oxaliplatin; diarrhea and hand-foot syndrome from capecitabine)?[19]
3. Are there targeted, small-molecule inhibitors that can be added to adjuvant chemotherapy to increase efficacy but not toxicity?
4. Can the group of stage-II patients who might benefit most from adjuvant chemotherapy be more clearly defined?
5. When sequencing the genome of an individual patient's tumor becomes practical, how will the ensuing data on genetic alterations in cancer cells be used to tailor adjuvant therapy in a patient-specific manner? ■

## References


1. Wolmark N, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: Results from the National Surgical Adjuvant Breast and Bowel Project protocol C-03. *J Clin Oncol* 1993 11:1879-1887.
2. O'Connell MJ, et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol*. 1997 15:246-250.
3. Marsoni S, et al. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. *Lancet*. 1995 345:939-944.
4. Andre T, et al. Phase III study comparing a semimonthly with a monthly regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: Final results of GERCOR C96.1. *J Clin Oncol*. 2007 25:3732-3738.
5. Twelves C, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med*. 2005;352: 2696-2704.
6. Andre T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004 350:2343-2351.
7. Andre T, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II and III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27:3109-3116.
8. Kuebler JP, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: Results from NSABP C-07. *J Clin Oncol*. 2007;25: 2198-2204.
9. Schmoll HJ, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: A planned safety analysis of 1,864 patient. *J Clin Oncol*. 2007;25:102-109.
10. Saltz LB, et al. Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant for stage III colon cancer: Results of CALGB 89803. *J Clin Oncol*. 2007;25:3456-3461.
11. Van Cutsem E, et al. Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3. *J Clin Oncol.* 2009; 27:3117-3125.

12. Wolmark N, et al. A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSAABP Protocol C-08 (abstract#4). *J Clin Oncol*. 2009;27:793s.
13. Sargent DJ, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med*. 2001;345:1091-1097.
14. Stein BN, et al. Age and sex are independent predictors of 5-fluorouracil toxicity. Analysis of a large scale phase III trial. *Cancer* 1995;75:11-17.
15. Goldberg RM, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol.* 2006;24:4085-4091.
16. McCleary NA, et al. Impact of older age on the efficacy of newer adjuvant therapies in > 12,500 patients with stage II/III colon cancer: findings from the ACCENT database (abstract #4010). *J Clin Oncol*. 2009 27:170s.
17. Grothey A, et al. Evaluation of the effect of intravenous calcium and magnesium on chronic and acute neurotoxicity associated with oxaliplatin: Results from a placebo-controlled phase III trial (abstract). *J Clin Oncol*. 2009 27:174s.
18. Nikcevich DA, et al. Effect of intravenous calcium and magnesium on oxaliplatin-induced sensory neuropathy in adjuvant colon cancer: results of the phase III placebo-controlled double-blind NCCTG trial N04C7 (abstract). *J Clin Oncol*. 2008 26:180S.
19. Ruzzo A, et al. Pharmacogenetic profiling in patients with advanced colorectal cancer treated with first-line FOLFOX-4 chemotherapy. *J Clin Oncol*. 2007;25: 1247-1254.

# Combination Oral Chemotherapy for Second-line SCLC

ABSTRACT & COMMENTARY

***By William B. Ershler, MD***

***Synopsis:*** *In a retrospective review of 71 patients treated in either a second- or third-line setting for small-cell lung cancer (SCLC) at a single institution, three orally administered drugs (lomustine, etoposide, and cyclophosphamide) were shown to be effective in producing responses (overall response rate 38%) but had little effect on overall survival (median survival 19 weeks). Grade 3/4 hematological toxicity was observed in about one third of the treated patients, and three patients died with neutropenic fever. Currently, in a randomized phase-II trial for second-line SCLC in patients underway in France, this regimen is being compared with conventional intravenous chemotherapy.*

**Source:** Lebeau B, et al. Oral second-line and third-line lomustine-etoposide-cyclophosphamide chemotherapy for small cell lung cancer. *Lung Cancer*. 2010;67:188-193.

SMALL-CELL LUNG CANCER (SCLC) REMAINS A HIGHLY-lethal disease despite high response rates to initial chemotherapy. Upon relapse, the response to second-line chemotherapy is likely to be higher in those with a good performance status and longer time to relapse. In fact, retreatment with the first-line regimen should be considered for those who relapse > 6 months after the end of initial treatment. Various chemotherapy regimens have been evaluated in the phase-II setting, but none has emerged as significantly more effective than the others.[1] Topotecan, administered orally as a single agent, has been shown to be superior to best supportive care (BSC),[2] and is currently the only drug licensed in the second-line setting. However, in this randomized, phase-III trial,[2] the partial response rate was only 7%. Nonetheless, disease stabilization was observed in 44%, and quality of life was measurably better, as was overall survival when compared with those receiving BSC. In contrast, Lebeau et al from Paris report their experience with an alternative three-drug oral regimen (lomustine, etoposide, and cyclophosphamide) used as second- or third-line therapy for patients with SCLC.

In this retrospective review, the data on 71 SCLC patients (36 treated as second line and 35 as third line) were analyzed. They received lomustine (CCNU) 80 or 120 mg on day 1 only, etoposide 100 mg from day 1 through day 6-14, and cyclophosphamide 100 mg from day 1 through day 6-14, every four weeks. The dosages of CCNU, and duration of administration of the other two drugs, were adjusted in a standardized way based upon age, performance status, weight, and hematological parameters. Evaluation, based on clinical status, response, and weekly blood counts, was performed before each cycle until progression.

The patients received between one and 20 cycles of treatment (mean = 3.7 for second-line and 3.0 for third-line treatment). Complete responses were observed for three patients in each line, and partial

responses were noted in 13 patients in second-line and eight patients in third-line therapy, resulting in a total response rate of 27/70 = 38%. Median survival time, estimated from the start of second- or third-line treatment, was the same in the two subgroups: 4.4 months. But, the patients in the two subgroups presented different clinical characteristics. Hematological toxicity was commonly observed, and three patients died with neutropenic sepsis. Furthermore, 39% had grade 4 neutropenia and 34% had grade 4 thrombocytopenia.

## ■ COMMENTARY

Although hematologic toxicity was common, this was not unexpected in this group of pretreated patients. The observed response rate is quite remarkable in this setting, but should be interpreted very cautiously, as it is derived from a single institution upon retrospective analysis. Furthermore, despite the response rates, overall survival, measured in weeks, was still quite dismal, and possibly less than observed with oral or intravenous topotecan. However, as the authors point out, the current report reflects the treatment of patients in both second- and third-line treatment, including those with poorer prognostic factors and poorer performance status.

Furthermore, this combination has the advantage of being orally administered and generally well tolerated. Whether it will become a standard second-line approach for SCLC will require clinical trials, and one such trial is currently underway in France. In the meantime, alternative therapies are emerging, offering even greater hope for this group of patients.[3] Currently under investigation are anti-angiogenic agents, growth factor receptor inhibitors, inhibitors of downstream signaling pathways and drugs that promote apoptosis. Among the latter, inhibitors of prosurvival Bcl-2 proteins are currently entering the clinical arena and are an exciting prospect aimed at combating drug resistance in first- and second-line treatment for SCLC. ■

### References


1. Hurwitz JL, et al. New advances in the second-line treatment of small cell lung cancer. *Oncologist*. 2009;14:986-994.
2. O'Brien ME, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol*. 2006;24:5441-5447.
3. Blackhall FH, Shepherd FA. Small cell lung cancer and targeted therapies. *Curr Opin Oncol*. 2007;19: 103-108.


# Lymphoma/Leukemia Risk among Morticians

ABSTRACT & COMMENTARY

***By William B. Ershler, MD***


***Synopsis:*** *Among funeral workers, the duration of embalming practice and related formaldehyde exposure were significantly associated with an increased risk for mortality from myeloid leukemia.*



**Source:** Hauptman M, et al. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *J Natl Cancer Inst*. 2009;101:1696-1708.


IT HAS BEEN LONG KNOWN THAT FORMALDEHYDE IS CARcinogenic, and surveys among those exposed (e.g., anatomists, pathologists, and morticians) have shown excess numbers of deaths due to lymphoma, leukemia, and other cancers.[1-3] In a recent analysis by the International Agency for Research on Cancer, formaldehyde was classified as a human carcinogen (group 1) on the basis of experimental observations in rodents and epidemiological studies of exposed groups.[4] However, the available epidemiological evidence for occupational exposure to formaldehyde and leukemia was insufficient to establish causality.

Thus, Hauptmann et al investigated the relation of mortality to work practices and formaldehyde exposure levels among these professionals to address cancer risk in the funeral industry. For this, professionals employed in the funeral industry, who died between January 1, 1960, and January 1, 1986, from lymphohematopoietic malignancies (n = 168) or brain tumors (n = 48), were compared with deceased matched-control subjects (n = 265) in regard to lifetime work practices and exposure to the funeral industry, which were obtained by interviews with next of kin and coworkers, as well as estimated levels of formaldehyde exposure. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by use of logistic regression.

Mortality from myeloid leukemia increased statistically significantly with increasing number of years of embalming ($p$ for trend = .020) and with increasing peak formaldehyde exposure ($p$ for trend = .036). Notably, mortality from myeloid leukemia was elevated among those who performed embalmings for more than 34 years (OR = 3.9, 95% CI = 1.2 to 12.5, $p$ = .024), who performed more than 3,068 embalmings (OR = 3.0, 95% CI = 1.0 to 9.2, $p$ = .057), and for those whose estimated cumulative formaldehyde

exposure exceeded 9,253 parts per million-hours (OR = 3.1; 95% CI = 1.0 to 9.6, $p$ = .047). Also of note, the exposures did not relate to lymphoma or brain cancer development.

## ■ COMMENTARY

Thus, in a case-control study in a cohort of deceased funeral-industry workers, those who died from lymphoma, lymphoid, or myeloid leukemia or brain cancer were compared with matched controls. The lifetime work practices and exposures to formaldehyde were obtained by interviews with next of kin and coworkers for each case and control. It was found that the duration of embalming practice and related formaldehyde exposures were associated with statistically, significantly increased risk for mortality from myeloid leukemia. No associations were observed for other lymphohematopoietic malignancies, and there were too few cases of brain cancer to ascertain a statistically significant association.

This was a carefully conducted epidemiological study established on the basis of duration and density of exposure to a relationship of formaldehyde with myeloid leukemia. Although the data were derived indirectly (from next of kin and from co-workers), the investigators employed very careful methodology, and derived equivalent information, from well-matched controls. Indeed, this technique of examining only one job type (embalming) and determining individual exposure levels by assessing subject-specific information provides a significant step forward when compared to prior studies in which associations rely on aggregated information for subjects exposed under a variety of different circumstances. For example, when compared to the broader cohort of subjects exposed to formaldehyde,[5] funeral-home workers who embalm had a longer duration and higher cumulative level of exposure but lower average intensity of exposure.

The authors pointed out that the survey was based upon embalming practices through the early 1980s and, thus, may not be representative of current patterns of work, particularly with reference to formaldehyde exposure. ■

### References


1. Harrington JM, Shannon HS. Mortality study of pathologists and medical laboratory technicians. *Br Med J*. 1975;4:329-332.
2. Blair A, et al. Epidemiologic evidence on the relationship between formaldehyde exposure and cancer. *Scand J Work Environ Health*. 1990;16:381-393.
3. Stroup NE, Blair A, Erikson GE. Brain cancer and other causes of death in anatomists. *J Natl Cancer Inst*. 1986;77:1217-1224.
4. Cogliano V, et al. Advice on formaldehyde and glycol ethers. *Lancet Oncol*. 2004;5:528.
5. Beane Freeman LE, et al. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: The National Cancer Institute Cohort. *J Natl Cancer Inst*. 2009;101:751-761.


## CME Question

6. **Patients with metastatic breast cancer and a high number of detected circulating tumor cells (CTCs) are most likely to have:**
   a. metastatic disease in bone alone.
   b. metastatic disease in bone and other organs.
   c. metastatic disease in liver alone.
   d. metastatic disease in liver, lungs and brain (but not bone).

7. **Which of the following features of lomustine, cyclophosphamide, and etoposide chemotherapy for second- or third-line small-cell lung cancer treatment were advanced by Lebeau et al as a result of their retrospective analysis?**
   a. Ease of administration (oral)
   b. Improved overall survival
   c. Minimal hematologic toxicity
   d. Reduced transfusion requirements

8. **The recent report of formaldehyde exposure among embalmers defined an exposure-related increased risk for which of the following tumor types?**
   a. Non-Hodgkin's lymphoma
   b. Myeloid leukemia
   c. Brain cancer
   d. All of the above
   e. None of the above

**Answers:** 6. (b); 7. (a); 8. (b)

## CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss the most recent information regarding diagnosis and treatment of various types of cancer;
- describe current prevalence/surveillance data and long-term follow-up results of chemotherapy/radiation regimens; and
- describe new advances in the field of oncology.

## In Future Issues:

**Colonoscopy and the Right Colon**

Clinical Briefs in
# Primary Care™
The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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## Prevention of diabetes: The long-term outlook

***Source:*** Diabetes Prevention Program Research Group; et al. *Lancet* 2009;374:1677-1686.

NUMEROUS RANDOMIZED CLINICAL trials show that a variety of interventions can prevent the development of type 2 diabetes (DM2) in subjects with prediabetes (i.e., impaired glucose tolerance, defined as a 2-hour post-load glucose of 140-199 mg/dL). Lifestyle interventions (i.e., intensive diet and exercise programs) are generally at least as effective as pharmacotherapy (e.g., metformin, rosiglitazone, orlistat). Some experts quibble with the term "prevent," preferring instead to indicate that our prediabetes interventions simply "delay" diabetes. Since persons at high risk for DM2 are likely to remain in a high-risk group indefinitely, the long-term picture of interventions to prevent DM2 is important.

The Diabetes Prevention Program (DPP) was one of the largest diabetes prevention trials ever performed. At 2.8 years, incidence of DM2 was reduced 58% with lifestyle, and 31% with metformin (compared to placebo). A recent report by the Diabetes Prevention Program Research Group provides a window of insight into data 10 years from the date of randomization.

Compared to placebo, subjects in the lifestyle intervention group had a 34% reduction in new onset DM2; the metformin group had an 18% risk reduction.

Follow-up of subjects enrolled in the DPP indicates a long-term risk reduction in development of DM2 attained with lifestyle or metformin intervention. Whether you call it prevention or delay, less DM2 at 10 years is a good thing. ■

## Does it matter how we lower LDL?

***Source:*** Taylor AJ, et al. *N Engl J Med* 2009;361:2113-2122.

BASED UPON A PRESUMED DIRECT relationship between LDL lowering and reduction in CV events for persons with vasculopathy, many clinicians enthusiastically embraced the combination of ezetimibe (EZT) and statins, especially when therapeutic LDL goals were difficult to attain with a statin alone. After the ENHANCE trial, which questioned the ability of EZT to effectively regress carotid atherosclerosis, clinicians began to rethink the issue, fueled additionally by disappointing data from trials of torceptrapib, an HDL-raising drug, which not only did not reduce CV events, but actually worsened CV risk, and was subsequently withdrawn from consideration for FDA approval.

A single clinical trial, the Coronary Drug Project, showed CV risk reduction with niacin in long-term follow-up. Because of adverse effects that limit more universal use of niacin, agents that were much better tolerated (like EZT) appeared to be a more suitable choice.

A clinical trial was performed to evaluate the comparative efficacy of extended-release niacin with EZT in persons with known coronary disease or with a CHD risk equivalent (e.g., DM). All subjects were already on a statin and had achieved an LDL < 100 mg/dL. Over 14 months, the performance of niacin to regress carotid intima-media thickness was significantly greater than EZT. Indeed, the incidence of CV events was significantly lower in the niacin group also (1% vs 5%).

Although EZT is effective in reducing LDL, it has not been shown to have a favorable effect upon CV or vascular surrogate endpoints; hence, its use must be reconsidered. ■

## Identifying risk factors for falls in seniors

***Source:*** Leveille SG, et al. *JAMA* 2009;302:2214-2221.

AMONG OLDER ADULTS, FALLS REMAIN in the top 10 causes of death. Risk factors for falls include vitamin D status, cognitive status, physical decline, and mobility impairment. The epidemiologic magnitude of fall risk has motivated the search for other risk factors.

Leveille et al studied a population of community-dwelling senior citizens (age > 70 years) in the greater Boston area. Each participant (n = 749) was assessed for chronic pain, and reassessed on a monthly basis for 18 months. During this interval, subjects reported 1029 falls.

Subjects were stratified into pain scores by tertile. Most pain syndromes were associated with disorders like osteoarthritis, and included individuals with a single painful area as well as multiple symptomatic sites.

There was a linear relationship between pain scores and risk for falls. Subjects with two or more painful sites had approximately 20% greater risk of falls when compared to persons without pain. Although one might think that analgesic use prompted by joint pain might explain a greater incidence of

falls, such a relationship was not demonstrable in this population.

Why pain is associated with falls is uncertain. Perhaps pain leads to deconditioning, leading to falls. There is also some support for cognitive effects of chronic pain that might lead to lesser executive alacrity, impairing the ability to respond to precipitants of a fall. It remains to be shown whether superior pain control will reduce fall risk. ■

## Resistance vs aerobic exercise and COPD

***Source:*** O'Shea S, et al. *Chest* 2009; 136:1269-1283.

COPD IS CURRENTLY THE 4TH MOST common cause of death in the United States. Other than smoking cessation, only oxygen therapy in late-stage disease has been shown to modify disease. Pharmacotherapy provides improvements in symptoms and pulmonary function tests, but has not been shown to alter disease progression.

Physical deconditioning is commonplace in COPD. Indeed, the pathologic phenomenon seen in COPD of dynamic hyperinflation — an even greater diminution in ability to utilize expiratory reserve during exercise than at rest — helps explain why COPD patients may lack enthusiasm for aerobic exercise. Resistance exercise trials indicate that COPD patients can improve muscle strength, but whether such improvements translate into incremental symptomatic benefit or ability to participate in activities of daily living is uncertain.

O'Shea et al performed a meta-analysis of 18 controlled trials employing progressive resistance exercises for COPD patients. The data show some benefits of resistance exercise in ability to rise from a sitting position and climb stairs; however, trials comparing aerobic training vs resistance training indicated more favorable outcomes for activities like cycling, and that resistance training added to aerobic training provides little if any additional benefit. Finally, studies that indicated resistance training benefits for activities of daily living were ranked as having higher risk of bias. More studies specifically addressing the effects of resistance training upon functionality in COPD are needed. ■

## Breast cancer outcomes and soy intake

***Source:*** Shu XO, et al. *JAMA* 2009;302: 2437-2443.

ESTROGEN (EST) IS FELT TO PLAY A role in the development of breast cancer (BCA), and modulation of estrogen is utilized as a treatment for BCA. Soy foods contain a large amount of phytoestrogens, which impact natural estrogen receptors. Soy components have also been shown to possess anticancer effects. Ultimately, whether dietary soy affects important outcomes like survival or progression of disease among subjects with cancers that may be estrogen-sensitive — like BCA — is critical to ascertain.

Shu et al studied data from the Shanghai Breast Cancer Survival Study, which provides a population of Chinese breast cancer survivors (n = 5042). After approximately 4 years of follow-up, the relationship between soy intake and BCA recurrence, overall mortality, and BCA-related deaths was evaluated. There was a consistent, linear, and inverse relationship between soy intake and mortality and BCA recurrence. When compared with persons in the lowest quartile of soy intake, those in the highest quartile enjoyed a 29% lower relative risk of mortality, and a 32% lower risk of BCA recurrence.

The relationship between soy intake and favorable outcomes was not altered by estrogen receptor-positive or -negative status or tamoxifen use.

Average soy intake in U.S. women (1-6 mg/day) is markedly less than Chinese women (47 mg/d). Whether incremental dietary soy increases in the U.S. population will translate into risk reduction has not been determined. ■

## Oxygen therapy for cluster headache

***Source:*** Cohen A, et al. *JAMA* 2009; 302:2451-2457.

THE PAIN OF CLUSTER HEADACHE (CLUS) is among the most severe of any clinical syndrome. The advent of triptans, especially sumatriptan injection, has restructured the landscape of CLUS management, since SQ sumatriptan has been shown to provide effective CLUS pain relief within 15 minutes. Unfortunately, since some patients with CLUS have multiple attacks per day, for multiple days, triptan dosing limitations preclude use in these high-frequency sufferers. Additionally, CLUS patients with CAD are unable to use triptans.

Another first-line CLUS treatment is high-flow oxygen (OXY). Advantageous aspects of oxygen treatment include its low adverse-effect profile, ability to be combined with other treatments, and applicability for multiple attacks within a short time frame. Despite commonplace clinical use, trial data on OXY are quite limited.

Cohen et al performed a randomized placebo-controlled study to compare 100% oxygen vs room air (both delivered at 12 L/min for 15 minutes). Study participants (n = 109) were followed for 5 years, with instructions to treat at least 4 attacks of CLUS with either OXY or placebo (room air). All subjects received indistinguishable separate tanks of 100% oxygen and room air, and were instructed to alternate tanks for sequential CLUS episodes in their home.

The primary endpoint of the study was percent of individuals pain-free at 15 minutes. OXY was much superior to air (78% vs 20% pain free). Randomized, placebo-controlled confirmation of our clinical practice supports continued appropriateness of OXY for CLUS. ■

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# Dabigatran: An Oral Direct Thrombin Inhibitor

***In this issue:*** Results from a Phase 3 study of dabigatran, intensive lipid-lowering in CVD, H1N1 vaccine dosing and efficacy, and FDA Actions.

## Anticoagulation without monitoring?

Dabigatran is an oral direct thrombin inhibitor, currently being used in many countries as an alternative to warfarin. It is anxiously awaited in this country primarily because, unlike warfarin, it does not require monitoring with blood tests. The drug has been shown to be as effective as warfarin in preventing stroke in patients with atrial fibrillation (*N Engl J Med* 2009;361:1139-1151).

A new study published in December 2009 compares the two drugs in the treatment of acute venous thromboembolism. In a randomized, double-blind, non-inferiority trial, patients with acute venous thrombus embolism were given a median of 9 days of parenteral anticoagulation therapy, then were randomized to oral dabigatran (150 mg twice a day) or warfarin that was dose-adjusted to achieve an INR of 2.0-3.0. The primary outcome was 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Of the patients randomized to receive dabigatran, 2.4% had recurrent venous thromboembolism compared to 2.1% of patients on warfarin (difference in risk of 0.4%; 95% confidence interval [CI], -0.8 to 1.5; $P < 0.001$ for the prespecified non-inferiority margin). Major bleeding episodes occurred in 1.6% of patients on dabigatran vs 1.9% of patients on warfarin. Episodes of any bleeding were 16.1% with dabigatran and 21.9% with warfarin. There was no difference in the number of deaths, acute coronary syndromes, or abnormal liver function tests between the two groups. Treatment was discontinued due to adverse events in 9% of patients on dabigatran and 6.8% of patients on warfarin. The authors concluded that for treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has similar safety, but does not require laboratory monitoring (*N Engl J Med* 2009;361:2342-2352).

Physicians and patients alike in the United States have been awaiting an orally effective anticoagulant that doesn't require monitoring. Dabigatran, a direct thrombin inhibitor, may soon fill that role. The drug, which has the additional advantage of having minimal drug and food interactions, has been available in Canada and Europe for almost 2 years, and with the completion of Phase 3 trials such as this one, there is speculation the FDA may take action this year. ■

## Intensive lipid-lowering and CVD

Follow-up analysis of two of the most famous lipid-lowering trials confirms that intensive lipid-lowering therapy continues to be beneficial in the longer term. The PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial, first published in 2004,

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compared moderate lipid-lowering using standard-dose pravastatin to intensive lipid-lowering with high-dose atorvastatin after acute coronary syndrome. The study showed high-dose therapy significantly reduced the occurrence of death, myocardial infarction, stroke, and unstable angina requiring hospitalization or revascularization occurring more than 30 days after the event. The new post-hoc analysis (*J Am Coll Cardiol* 2009; 54:2358-2362) followed patients for up to 2 years and showed continued benefit in reduction of the primary endpoint (16%; $P$ = 0 .005) with high-dose therapy, as well as reduction of additional events (19%; $P$ = 0.009).

The IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study compared high-dose atorvastatin with usual dose simvastatin for the prevention of events subsequent to a first event. The study was published in 2005, and while not showing reduction in mortality in the 4.8 years of study, it did show a reduction in secondary cardiovascular outcomes with high-dose therapy. The new analysis looked at not only time to first event, but also second, third, fourth, and fifth events. High-dose therapy significantly reduced subsequent events by 17%-28%. The authors concluded that continued intensive statin therapy continues to be more effective than standard statin therapy, even beyond the first vascular event (*J Am Coll Cardiol* 2009;54:2353-2357).

Both these studies suggest that staying the course with intensive lipid-lowering in patients with cardiovascular disease is an effective long-term strategy. ■

## H1N1 dosing and efficacy

Three recent studies in the Dec. 17, 2009, *New England Journal of Medicine* confirm that a single dose of the H1N1 vaccine is effective for most healthy adults and children age 3 and older. In the first study, 240 patients were equally divided to receive 15 µg or 30 µg of hemagglutinin antigen by IM injection. By day 21, antibody titers of 1:40 were observed in 95.0% of patients who received the 15 µg dose and 89.1% of patients who received the 30 µg dose (*N Engl J Med* 2009;361:2405-2413).

In the second study from China, antibody titers were done at 21 days after a first injection of 15 µg with or without adjuvant. A titer of 1:40 was achieved in 75% of subjects between age 3 and 11, 97.1% of subjects between age 12 and 17, 97.1% of subjects between age 18 and 60, and 79.1% of subjects age 61 and older. Alum adjuvant did not significantly raise antibody titers. Although a second injection at 21 days raised antibody titers, the authors conclude that a single dose of 15 µg induced a typically protective antibody response in the majority of subjects between age 12 and 60 (*N Engl J Med* 2009;361:2414-2423).

In the third study, standard H1N1 vaccine was compared to a MF59-adjuvanted vaccine (derived from cell culture rather than egg-based). A number of injection schedules were tested. Local reactions and muscle aches were more frequent in the MF59-adjuvanted vaccine. Although higher antibody titers were seen with the adjuvanted vaccine, significant titers were also seen within non-adjuvanted vaccine within 2-3 weeks (*N Engl J Med* 2009;361:2424-2435).

These findings confirm data previously published in the *Lancet* in the fall of 2009 confirming that one dose of the H1N1 vaccine seems adequate, although two doses may be required for younger children. Currently, the Centers for Disease Control and Prevention (CDC) recommends two doses for children younger than age 10, but the recommendations may change based on these findings.

In related news, the CDC is reporting that safety data regarding the H1N1 vaccine is "reassuring," with a rate of serious complications such as Guillain-Barré syndrome no higher than "background rates." The rate of adverse event reporting has been higher with the H1N1 vaccine compared to seasonal flu; however, most of these reports have been for mild reactions and may be attributed to the higher rate of awareness associated with the new vaccine. ■

## FDA Actions

The FDA has approved the first generic version of donepezil (Aricept®) for the treatment of Alzheimer's disease. The new generic will be marketed as 5 mg and 10 mg orally disintegrating tablets, which dissolve on the tongue and do not need to be swallowed. Generic donepezil is expected to be available later this year. ■

An FDA advisory panel is recommending expansion of the indication for rosuvastatin (Crestor®) to include patients with normal cholesterol levels and no history of cardiovascular disease. The recommendation is based on the JUPITER trial, which showed a reduction in cardiovascular risk in patients with normal LDL cholesterol but high C-reactive protein who were treated with rosuvastatin. ■