



E & N News to Use *for cancer patients, survivors and caregivers*

EXERCISE & NUTRITION during/after* *CANCER*

CURRENT PEER-REVIEWED MEDICAL LITERATURE and EXPERT COMMENTARY
from RELIABLE SOURCES and DR. BLEYER

*Studies on cancer prevention are included if they have special relevance to cancer survivors

February 2010

The 12 months of 2009 *E&N News* are now available as a **year summary** for downloading, either for exercise or nutrition (with each including reports on the combination of exercise and nutrition) at www.DEFEATcancer.info. Both versions have executive summaries and are indexed and bookmarked.

E&N News is now listed as **one of 7 resources recommended by MD Anderson Cancer Center** in the *Complementary Therapies, General* category and endorsed by the Cancer Patient Education Network of the National Cancer Institute. The MD Anderson Cancer *Complementary/Integrative Medicine Educational Resources* resource (www.mdanderson.org/departments/CIMER) is rated #1.

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► Exercise

Promising homeopathy for mucositis fails trial

[Alternative medicine trials are fraught with challenges](#)

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accessed February 15, 2010

By Ted Bosworth

New York—Despite a previously published pilot study that had positive outcomes, an alternative medicine for mucositis called traumeel was shown to be ineffective in children in a multicenter, double-blind trial conducted by the Children’s Oncology Group (COG). The study was a rare effort to subject alternative medicines, which are now widely used by cancer patients, to the same rigorous, evidence-based examination used for conventional treatments.

According to Edward Chu, MD, chief of medical oncology and director of clinical research at Yale Cancer Center, New Haven, Conn., research groups that want to test botanical herbal medicines in clinical trials face unique challenges because many of these medicines are complex agents. Generally, standard Western anticancer therapies consist of a single active agent that must be titrated into a therapeutic window in which the agent is both tolerable and active. In contrast, the large majority of therapies derived from botanicals are made up of multiple components for which the composition ratio may be critical. “The agent in the study conducted by the COG has at least 14 different ingredients that may be important for the activity of the agent. In approaching these agents, ensuring the consistency of the source and preparation is challenging but essential for an adequate test of clinical efficacy,” said Dr. Chu, who was not involved with the study. He said one explanation for the highly positive pilot study and the negative multicenter study is that the second study used a version of traumeel that was in fact quite different from the original.

Rigorous Testing of Homeopathies

Although the lack of benefit from traumeel was a disappointing first attempt by COG to validate complementary therapies in oncology, the fact that COG even conducted a clinical trial with the agent is a big thing in itself. “With lots of scientific soul searching, COG did agree that it should become involved in testing alternative medicines, not least because so many patients are taking them,” said

Susan F. Sencer, MD, medical director of Hematology/Oncology at Children’s Hospitals and Clinics of Minnesota in Minneapolis, who led the study of traumeel. Presenting the results of the study at the recent annual meeting of the Society for Integrative Medicine in New York City, Dr. Sencer reported that traumeel was a reasonable candidate for study in a large multicenter trial because there was abundant evidence that the drug is safe; there was preliminary evidence of efficacy from a controlled pilot study; and current treatments of mucositis offer little benefit.

Traumeel is considered a complex homeopathic agent, because it is a combination of defined and measurable ingredients that are believed to act together to exert its effect. This therapy has been widely used by homeopaths to treat a variety of indications, particularly inflammatory diseases. A controlled trial demonstrating the efficacy of traumeel in mucositis was published in a peer-reviewed journal in 2001 (Cancer 2001;92:684-690, PMID: 11505416). Although this study randomized only 32 patients, it was double-blinded and used an objective scoring system to compare efficacy of the homeopathy with placebo. In the study, traumeel reduced the risk for mucositis by almost 30% (67% vs. 93%) and prevented the likelihood that those who had mucositis would develop a more severe case by roughly 50% (47% vs. 93%).

The interest in traumeel after this study was published led the National Cancer Institute (NCI) to fund the COG study to see if these results could be replicated. Although Dr. Sencer acknowledged that she was not

initially receptive to the idea of conducting a study of an alternative medicine, she and others participating in COG have accepted that such therapies, now used in up to 90% of cancer patients, deserve to be studied when there is at least some existing support for efficacy and safety. The published evidence of benefit in mucositis, for which no therapy has been particularly effective, provided the justification for a large study of traumeel.

Study Details

In the COG study, 190 patients at 26 participating centers in several countries were randomized to receive either traumeel or placebo. Patients between the ages of 3 and 25 years receiving a myeloablative regimen for stem cell transplantation were eligible. The primary outcome was the severity of mucositis as measured with the World Health Organization (WHO) scoring system, which was used in the previous trial, and with a scoring system developed by the COG. Secondary outcomes included narcotic use and need for total parenteral nutrition. On their assigned therapy, patients were required to rinse their mouth vigorously for 30 seconds before swallowing. This was repeated five times per day, and patients were told to avoid food or drink for 30 minutes after each dose.

Although Dr. Sencer noted that the trial had one of the most rapid accruals in the history of COG, presumably because of interest in alternative therapies for mucositis, compliance with the regimen proved to be difficult; 66 patients dropped out before the study was completed. Dropouts occurred as frequently on placebo as on active treatment. Although the patients remaining in the study provided adequate power to detect a difference, none was found. This was true of both the primary and secondary end points except for a small and nonsignificant trend for reduced narcotic use in the traumeel group. Post-hoc analyses in which patients were stratified by varying levels of compliance also failed to show any advantage of traumeel. **“We looked at the data at all angles and really did not find any difference,”** Dr. Sencer said.

Trials Are Complicated

According to Dr. Chu, testing homeopathies in clinical trials is more complicated than testing standard drugs. “The importance of the complexity of botanical and traditional medicines is not very well understood by those used to working with standard pharmaceuticals,” said Dr. Chu, who has been active in evaluating traditional Chinese medicines for cancer care. Ensuring the composition of a homeopathy is difficult. He emphasized that quality control is a major issue, but he and others have had success in establishing highly sophisticated chemical and biologic fingerprint profiling methodologies to ensure consistency across batches. With his colleagues at Yale Cancer Center, Dr. Chu has conducted a series of pilot studies with a particular Chinese herbal medicine called PHY906, and they have demonstrated promising efficacy as a modulator of chemotherapy-induced toxicities in several gastrointestinal cancers. “I think the FDA feels uncomfortable with agents that have more than six active components. At our center, we are looking at a Chinese herbal medicine that is made up of four main herbs. However, using a very sensitive LC-MS [liquid chromatography-mass spectrometry] method, we have now identified at least 64 individual molecules contained within these four main herbs, which highlights the complexity of these herbal medicines,” Dr. Chu said. He believes the FDA may come to accept the complex composition of alternative agents, but he still expects the agency to insist on a rigorous analysis capable of providing characterization of the herbal formulation to ensure that it is reproducible. Dr. Chu believes these drugs should be subjected to the same types of rigorous clinical trials that have established the safety and efficacy of traditional Western therapies.

Because of the difficulties of compliance and inadequate information about appropriate dose, traumeel was not proven inactive in the COG study. Instead, the study conclusion was that it cannot be considered an evidence-based therapy for mucositis in children, according to Dr. Sencer. However, despite these disappointing results, Dr. Sencer said that COG will undertake clinical studies of other alternative agents if pilot studies provide an expectation of efficacy and safety.

“COG is committed to the study of any therapy that will improve management of pediatric cancer,” said Dr. Sencer, who characterized **the large, controlled studies as “the final common pathway”** for establishing the clinical viability of treatments in cancer. Dr. Chu did not disagree, but he suggested that

lack of understanding of the nature of these therapies combined with baseline skepticism increases the likelihood of failed trials. He suggested that the study of these botanical medicines requires a different approach that places an emphasis on recognizing and preserving the active ingredients. He believes this field is highly promising, but consistent results across trials require that the quality and consistency of the study agent be initially established.

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Dr. Bleyer:

- ☑ Last month, E&N News published an extensive review of the clinical effects of botanicals, as presented at the St. Charles Medical Center Grand Rounds in January 2010
- ☑ As a Children's Oncology Group investigator, Dr. Bleyer was involved with the planning of this trial, and as and Medical Director of the University of MD Anderson Cancer Center Community Clinical Oncology Program Research Base, he helped develop clinical trials of acupuncture, nutritional supplements, and mindfulness relaxation
- ☑ Dr. Bleyer is not surprised at the lack of benefit of traumeel and its 14 homeopathic ingredients, despite 5 applications every day, given the small size of the preliminary trial that led to the definitive one and the subjective nature of the measurements in the original trial
- ☑ Many cancer chemotherapeutic agents that have been selected for testing in large trials based on preliminary evidence for effectiveness have been similarly found to be ineffective
- ☑ This is exactly why prospective clinical trials are necessary; without them we would never have been able to eliminate what doesn't work and advance the field like we have; virtually everything we know about treating cancer came from clinical trials

► Nutrition

Metabolic syndrome, central obesity and insulin resistance are associated with adverse pathological features in postmenopausal breast cancer

[Breast cancer patients who are overweight and have a diabetic tendency \(metabolic syndrome\) may not only have developed their cancer in part because of the syndrome but are more likely to have a worse kind or more advanced breast cancer](#)

Healy LA, Ryan AM, Carroll P, Ennis D, Crowley V, Boyle T, Kennedy MJ, Connolly E, Reynolds JV. Department of Clinical Nutrition, St James's Hospital and Trinity College Dublin, Ireland. Clin Oncol (R Coll Radiol). 2010 Feb 25. [Epub ahead of print]

AIMS: Obesity is associated with both an increased risk of postmenopausal breast cancer and increased mortality rates. The mechanism is unclear, and central (visceral) obesity, insulin resistance, altered sex steroids and altered adipokines are mooted as possible factors. These features may cluster in the so-called metabolic syndrome. The relevance of metabolic syndrome to the biology of breast cancer is unknown, and this was the focus of the present study.

MATERIALS AND METHODS: All postmenopausal women with newly diagnosed breast cancer (n=105) were recruited. A detailed clinical history was carried out, as well as a body composition analysis, metabolic screen and measurement of adipokines and inflammatory markers.

RESULTS: The median age was 68 years (40-94 years) and the mean body mass index was 28.3+/- 5.2kg/m(2), with 87% of patients centrally obese. Metabolic syndrome was diagnosed in 39% of patients, and was significantly associated with central obesity (P<0.005) and increased inflammation, with C-reactive protein levels doubling in metabolic syndrome patients compared with non-metabolic syndrome patients (10.3 vs 5.8mg/l; P=0.084). Patients with a later pathological stage (II-IV) were significantly more likely to be obese (P=0.007), centrally obese (P=0.009), hyperglycaemic (P=0.047) and hyperinsulinaemic (P=0.026); 51% had metabolic syndrome compared with 12% for early stage disease. Patients with node-positive disease were significantly more likely to be hyperinsulinaemic (P=0.030) and have metabolic syndrome (P=0.028) than patients with node-negative disease.

DISCUSSION: The data suggest that metabolic syndrome and central obesity are common in postmenopausal breast cancer patients, and that metabolic syndrome may be associated with a more aggressive tumour biology.

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Dr. Bleyer:

- ☑ With just 105 patients in this study, the degree of correlation of the more advanced stage with metabolic syndrome is striking (the P- values are in the range of 99 out of 100 chance that the finding is real (and not due to chance)
- ☑ Having metabolic syndrome is a double whammy in not only being at greater risk of developing cancer but in having a worse kind when it does occur
- ☑ For breast cancer, it's a triple whammy since patients with metabolic syndrome are more difficult to treat, as reported in prior issues of *E&N News*

Prediagnosis food patterns are associated with length of survival from epithelial ovarian cancer

In patients with ovarian cancer, the length of survival is correlated with the nutrition prior to diagnosis; the more fruits and vegetables the better, the more meat the worse

Dolecek TA, McCarthy BJ, Joslin CE, Peterson CE, Kim S, Freels SA, Davis FG.
J Am Diet Assoc. 2010 Mar;110(3):369-382.

BACKGROUND: Dietary factors have been the focus of many studies on the etiology of ovarian cancer and may potentially affect survival. Indeed, three recent studies outside the United States have suggested that diet plays a role in ovarian cancer survival.

OBJECTIVE: The study purpose was to evaluate the hypothesis that women diagnosed with ovarian cancer whose reported prediagnosis food patterns more closely reflect recommendations for optimal health experience a survival advantage compared with those reporting poorer diets. **DESIGN:** A longitudinal follow-up study design was used to examine prediagnosis usual diet effects on survival among 341 Cook County, Illinois, residents diagnosed with epithelial ovarian cancer during 1994-1998. These women participated in a previous case-control study where diet was assessed using a validated food frequency questionnaire. This diet information was categorized utilizing the Dietary Guidelines for Americans 2005. Deaths through 2005 were ascertained using a national death index search. **STATISTICAL ANALYSIS:** Hazard ratios (HR) and 95% confidence intervals (CI) adjusting for important covariables were obtained from proportional hazards regression models to evaluate diet effects on survival from ovarian cancer.

RESULTS: Comparisons of high to low food group or subgroup intakes demonstrated statistically significant prediagnosis food pattern associations with survival time. Longer survival was associated with total fruits and vegetables (HR 0.61, 95% CI 0.38 to 0.98, P for trend=0.10) and vegetables separately (HR 0.66, 95% CI 0.43 to 1.01, P for trend <0.05). Subgroup analyses showed only yellow and cruciferous vegetables to significantly favor survival. Conversely, a survival disadvantage was shown for meats, not generally recommended (HR 2.28, 95% CI 1.34 to 3.89, P for trend <0.01), and specifically the red and cured/processed meats subgroups. An increased HR was also observed for the milk (all types) subgroup (HR 2.15, 95% CI 1.20 to 3.84, P for trend <0.05).

CONCLUSIONS: Prediagnosis adherence to diets that reflect recommendations for optimal nutrition and cancer prevention may have benefits that continue even after an ovarian cancer diagnosis.

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Dr. Bleyer:

- ☑ The importance of this study is that the patient's diet *before* diagnosis was predictive of how the patient did after treatment was started
- ☑ The study did not include the diet after diagnosis and thus cannot soundly conclude that pre-diagnosis nutrition was a major factor in the survival difference; it is very likely that dietary habits were the same before and after diagnosis and therefore post-diagnosis fruit and vegetable consumption (and less meat consumption) could be the more important factor
- ☑ And as **DEFEATcancer** repeatedly notes, physical activity was not assessed; since it is likely that patients with the more favorable diets also exercise more, the survival difference may also be due to physical activity, and even more likely, to a combination of diet and exercise (**DEFEAT**).
- ☑ Until more evidence exists, diet and exercise can be considered to be important before, during and after a cancer diagnosis, and ultimately a lifelong need

Relationships between cardiorespiratory fitness, physical activity, and psychosocial variables in overweight and obese breast cancer survivors

Physical activity alone did not significantly improve psychological status of women with breast cancer

Taylor DL, Nichols JF, Pakiz B, Bardwell WA, Flatt SW, Rock CL.
Int J Behav Med. 2010 Feb 23. [Epub ahead of print]

BACKGROUND: Breast cancer survivors not only experience distressing physical symptoms associated with treatments, but also are faced with psychosocial challenges. Despite growing scientific evidence that physical activity (PA) may mitigate psychosocial distress experienced by women treated for breast cancer, the literature is equivocal.

PURPOSE: This study investigated the relationships between cardiorespiratory fitness (CRF), PA, and psychosocial factors in breast cancer survivors.

METHOD: Data involving overweight or obese breast cancer survivors (N = 260) were examined. CRF was determined by a submaximal graded exercise test. PA, depressive symptoms, total fatigue, and global self-esteem were assessed with self-report measures. Pearson's correlations were conducted to determine associations among CRF, PA, depressive symptoms, total fatigue, and global self-esteem. Multiple regression models, with age and body mass index as covariates, were performed using continuous levels for CRF and PA.

RESULTS: Bivariate correlations suggested that CRF and PA were unrelated to the psychosocial variables. One of the regression models identified a marginally significant (P = 0.06) inverse association between depressive symptoms and PA.

CONCLUSION: CRF and PA were not associated with psychosocial factors in this sample of breast cancer survivors. However, minimal PA was reported by the majority of participants, so low PA variability likely influenced these findings.

Dr. Bleyer:

- ☑ With one potential exemption, this relatively large study (260 patients) did not find that those women who exercised the most had significantly less psychosocial challenges
 - ☑ As pointed out by the authors, the patients they studied (in San Diego) were relatively sedentary (minimal physical activity in a majority of patients) which limited the ability of the study to assess higher levels of exercise
 - ☑ Most of the patients were Hispanic, in whom exercise levels are known to be low and obesity prevalent
 - ☑ Nonetheless, the exception was depression, which had a 96 in 100 chance of truly being worse in those patients with less activity
 - ☑ Again, **DEFEATcancer** points out that nutrition was not assessed, and it is likely that, given the study population, was relatively poor; if **DEFEATcancer** is correct, the combination of diet and exercise (**DEFEAT**) is more important than either diet or exercise alone
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