Acupressure and Acupuncture for Side Effects of Radiotherapy

“Many symptoms of cancer patients, including pain, nausea, and dry mouth, are significantly different in an objective sense than in a subjective sense,” says Peter Johnstone, MD, William A. Mitchell Professor and chair of Radiation Oncology at the Indiana University School of Medicine. “We have evidence now proving that a disconnect often exists between a patient’s reported symptoms and objective evidence of those symptoms,” says Dr. Johnstone, who is also past president of the Society for Integrative Oncology. He made his comments in response to 2 recent studies regarding the effects of acupressure/acupuncture on nausea and xerostomia (dry mouth) in patients receiving radiotherapy for cancer.

Nausea is a common problem for patients undergoing cancer therapy. Several lines of research have documented that expectation of nausea before the administration of chemotherapeutic drugs influences the development of nausea during and after treatment. A group of investigators based at the James P. Wilmot Cancer Center recently set out to determine whether acupressure bands, which previously were shown to reduce chemotherapy-related nausea, also reduce radiation-induced nausea (J Pain Symptom Manage. 2009 March 27. [Epub ahead of print]). They also tested the hypothesis that an informational manipulation designed to enhance expectations regarding the efficacy of acupressure bands would, in fact, enhance the efficacy of the bands.

This group of investigators previously conducted 2 similar studies. In the first study, patients starting chemotherapy received educational material designed to dispel common misconceptions regarding chemotherapy-induced nausea. The intervention was successful in reducing the expectation of nausea in the patients randomized to receive the educational materials, but these patients did not appear to have less nausea during treatment than the control group that did not receive the educational intervention (J Pain Symptom Manage. 2008;35:381–387).

The investigators’ explanation of these results was that either the expectation of nausea is not truly related to its subsequent occurrence and perception, or that the intervention’s effect on expectation was not strong enough to influence subsequent nausea. In the second study, patients who were about to start chemotherapy were randomized to receive an acupressure band or an acustimulation band, both of which stimulated the P6 point on the inner wrist, an acupuncture point that has been reported to be associated with nausea relief. A control group received no intervention. Among the patients in this study, those who used acupressure bands and who reported that they expected them to be effective were found to have significantly less nausea than patients with acupressure bands who did not expect them to be effective, patients who received acustimulation bands, and patients who received no bands, suggesting that expectation was 1 factor that played a strong role in determining efficacy (J Pain Symptom Manage. 2003;26:731–742).

Patients were eligible for the current study if they had received a minimum of 2 radiation treatments and had experienced nausea/vomiting (NV) after at least 1 radiation session. Patients were asked to wear the acupressure band (Sea–Bands; Sea–Band Ltd, Hinckley, Leicestershire, UK) for 1 minute. Investigators explained that 2 things were being investigated: the efficacy of the bands and the way in which information about the bands was delivered to patients. After wearing the bands for 1 minute, patients took them off and completed a quality-of-life (QOL) measure and a questionnaire that included questions related to expected efficacy. Patients did not take the acupressure bands home, but they were given a take-home diary in which to record NV after their next 2 radiation treatments; this served as a baseline measure of NV. Study subjects were unaware of the study’s primary hypothesis that expectations would influence perceptions of efficacy.

When patients returned the diary of baseline NV symptoms, they were randomized to 1 of 3 groups:
Arm 1: Standard care.
Arm 2: Standard care plus acupressure bands plus information regarding the bands that was not intended to enhance expectations about the efficacy of the bands. Patients were informed about the investigators’ prior acupressure/acustimulation study, with the explanation that although patients who used the acupressure/acustimulation bands experienced less nausea than patients who did not get the bands, the difference “was probably due only to a placebo effect.” Visual material was printed on a gray scale.
Arm 3: Standard of care plus acupressure bands plus information regarding the bands that was intended to enhance expectations about the efficacy of the bands. Patients were presented with the results of both prior studies printed in full color, with an emphasis on positive results regarding the efficacy of acupressure for nausea induced by chemotherapy. For example, they were told “Only 3 patients wearing Sea–Bands had nausea compared to 15 patients not wearing Sea–Bands” and “Patients wearing Sea–Bands had less severe nausea on the day they received their chemotherapy.”

The patients in Arms 2 and 3 were instructed to wear 1 or both bands at their discretion over the next 5 days, during which time they received 5 radiation treatments. Antiemetic medications and other treatments for NV were permitted for patients in all 3 arms and were not standardized. Patients continued to record NV in a 5-day diary and completed a QOL questionnaire before going to bed after the fifth treatment.

NV were assessed with a patient report diary, in which patients reported on the severity and number of episodes of NV in the morning, afternoon, evening, and night of each radiation treatment. Investigators also assessed the amount of antiemetic medication taken by each patient. Each patient’s expectation of nausea was assessed by a questionnaire. QOL was measured with the Functional Assessment of Cancer Therapy Scale–General (FACT–G), a well-characterized and validated, 28-item scale. The investigators planned to determine the change in average nausea between baseline and after treatment using analysis of variance. A total of 99 patients were randomized, and 88 (89%) provided usable data. The baseline differences in nausea between the 3 treatment arms were significant and required the use of change scores in all subsequent analyses.

Patients who used the bands (Arms 2 and 3 combined) had a 23.8% reduction in the self-reported nausea score compared with a 4.8% decrease in the control group \( (P = .01) \). However, there were no differences noted between patients using bands and those not using the bands with regard to change scores of QOL \( (P = .93) \), changes in the daily amount of antiemetic medication used \( (P = .78) \), or changes in the occurrence of vomiting \( (P = .17) \). Nonetheless, satisfaction with the bands was high, with most patients reporting that they would recommend the bands to others undergoing radiotherapy.

The investigators did not find a difference in expected band efficacy between Arms 2 and 3 \( (P = .56) \). One explanation they suggested is that information that the investigators believed was neutral was actually perceived by the patients as positive. In particular, patients may not have recognized that calling the effect of the acupressure bands “just a placebo response” was dismissive and negative. In a follow-up study, Joseph A. Roscoe, PhD, research associate professor in the Department of Radiation Oncology at the University of Rochester Medical Center and the other investigators plan to simply thank patients in Arm 2 for their participation rather than attempting to present them with neutral educational information. “We think the difference [between neutral and positive information] in this context is just too subtle,” he says.

Among the 59 patients who used bands, the expected efficacy was not found to be correlated with the change in nausea \( (P = .61) \) or vomiting \( (P = .56) \). “It is possible, ” the investigators wrote, “that the acupressure bands were effective in our study for reasons not related to expectancy…that the acupressure bands are indeed efficacious, as suggested by a growing body of literature showing that stimulation of acupuncture points can indeed reduce nausea. It has, after all, been a staple of Chinese medicine for centuries. While our data support this interpretation, we are reluctant to accept it at face value because of other reports in the literature, including our own, linking the efficacy of acupressure bands to expectancy/placebo effects.”

“It appears that the acupressure bands are helpful in many patients, but not everyone,” says Dr. Roscoe. He noted that once nausea is established in patients, as it was in this group, it is hard to remedy it. “But that’s what happened here—established nausea was improved. It is preferable to prevent nausea in the first place,” he added.

“Some antinausea medications are very expensive, so a low-cost intervention like acupressure bands would be great for patients who need nausea relief,” Dr. Johnstone says. The only
caveat, says Dr. Roscoe, is that patients with lymphedema should be careful not to use the band on the affected arm.

Xerostomia occurs as both a chronic and acute complication of radiation administered in the treatment of head and neck cancer. In addition to mouth pain and difficulty speaking resulting from xerostomia, alterations in taste and difficulty swallowing can compromise nutritional status, and changes in the oral flora can lead to dental caries and even jaw infections. Investigators at The University of Texas M. D. Anderson Cancer Center in Houston conducted a pilot study to evaluate the effect of acupuncture on radiation-induced, self-reported xerostomia and, as a secondary objective, the effect of acupuncture on salivary flow rate (Head Neck. 2009 April 17. [Epub ahead of print]). Xerostomia tends not to resolve spontaneously, and the currently available methods used to manage the condition, including oral pilocarpine, electrical stimulation of oral tissue, and hyperbaric oxygen therapy, have limited efficacy and limited acceptance by patients. Early studies have suggested that acupuncture might stimulate saliva production in people with xerostomia induced by radiotherapy, which led this research team in Houston to conduct their study.

Nineteen patients participated; all had completed a course of bilateral, external-beam radiotherapy (>4000 centi-grays) at least 4 months before enrollment and had developed xerostomia afterward. The intervention consisted of acupuncture treatment given twice a week for 4 weeks. Five standard acupuncture sites were selected based on efficacy suggested by earlier studies with xerostomia.

Patients also completed a Xerostomia Inventory (XI) and a Patient Benefit Questionnaire (PBQ). “Both questionnaires assess symptoms related to dry mouth. They are scored differently, however,” says M. Kay Garcia, DrPH, MSN, a clinical nurse specialist and study coauthor. “For the XI, a high score indicates worse xerostomia and for the PBQ, a low score indicates worse xerostomia. We used both instruments in order to be sure we were measuring what we intended to measure and ensure validity of the assessment.” Patients also completed The Functional Assessment of Cancer Therapy Scale–Head and Neck (FACT–H&N) scale. “This QOL instrument asks some questions related to dry mouth, but it also assesses symptoms related to pain, fatigue, nausea, and the impact these have on functional, emotional, and social well-being,” Dr. Garcia explained.

The investigators also assessed the unstimulated whole salivary flow rate (UWSFR) and stimulated salivary flow rate (SSFR). Baseline determinations were made 1 week before the acupuncture intervention and then repeated at Weeks 1, 2, 3, 4, 5, and 8.

In these patients, the XI and PBQ scores were found to be significantly improved by acupuncture at Weeks 4 and 8 compared with baseline (XI: $P = 0.004$ and $P = .001$, respectively; and PBQ: $P = .0004$ and $P = .0011$, respectively). The FACT–H&N total scores were found to be significantly ($P = .03$) improved at Week 8. The authors concluded that acupuncture could improve the subjective symptoms of dry mouth and that these effects persisted for at least 1 month after acupuncture treatment. Despite these subjective improvements, the investigators found no change in the SSFR or UWSFR in these patients.

Dr. Garcia explained the difficulty in taking the salivary flow findings at face value: “Both basal and stimulated salivary flow rates vary significantly among individuals. UWSFR have been reported to range from 0.08 to 1.83 mL/minute, a difference of more than 20-fold. SSFR vary even more, from 0.2 to 5.7 mL/minute. Within this wide range of flow rates, subjective perception of dry mouth and objective signs of salivary gland dysfunction do not correlate,” she says.

Given the wide range of flow rates among patients with normal oral function, the assessment of salivary gland function without individual subject baselines is difficult, Dr. Garcia says. “Subjective sensations of oral dryness are not reliable indicators of flow rate; impaired salivary gland function can exist without xerostomia, which can, conversely, exist with normal salivary gland function. A difficulty lies in the fact that there is no definitive threshold of increased saliva output that results in a clear clinical benefit. Thus, the only benefit currently recognized by the FDA [US Food and Drug Administration] for approval of xerostomia therapies is the subjective response,” she adds.

“Acupuncture is a relatively low-cost intervention that is more widely available than people generally assume,” says Dr. Johnstone, who echoed Dr. Garcia’s observations that objective data regarding xerostomia are difficult to obtain, making the patient’s subjective reports the ones that really count.

“It’s how the patient feels that counts,” says Dr. Johnstone. “For many symptoms of cancer treatment—pain, dry mouth, nausea, and others—management involves a richer canvas than we’ve seen before.”

Dr. Johnstone adds that “Acupuncture and acupressure represent low-cost, but highly engaging mechanisms for potential relief of many cancer patients’ symptoms. Al-
though proper controls often are difficult in clinical trials investigating such integrative therapies, well-designed studies are ongoing in many centers.

Patients should discuss such nontraditional therapies with their oncologists prior to investigating them, but an increasing number of physicians are aware of appropriate community resources. Guidelines are available from the Society for Integrative Oncology for patients who are interested in using integrative therapies for cancer symptom control."

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**Human Papillomavirus Genotype Distributions Inform Screening and Vaccination Policy**

Interventions for cancer prevention are typically divided into 2 broad categories: primary prevention involves preventing the disease before it develops and secondary prevention involves the detection and treatment of precursor lesions and presymptomatic cancer. Prevention of cervical cancer has largely emphasized the Papanicolaou test for secondary prevention, with the combination of cytology plus testing for carcinogenic human papillomavirus (HPV) types recently added as an option. The recent availability of a vaccine against 2 carcinogenic HPV subtypes has made the primary prevention of most cervical cancer a possibility. HPV vaccination is expected to substantially change the prevalence of infection with carcinogenic HPV subtypes among individuals who receive the vaccine and, to a lesser degree, within the entire population. But how will these changes influence the future of secondary prevention programs?

With this question in mind, investigators based at the University of New Mexico Health Sciences Center in Albuquerque used data from the New Mexico Surveillance, Epidemiology, and End Results (SEER) registry to conduct a case–control study of HPV infection and cervical cancer risk (J Natl Cancer Inst. 2009;101:475–487). More specifically, they described cervical cancer risk according to HPV genotype and patient age.

“Our goal with this study was to examine what was happening in the population over time prior to the HPV vaccine being administered as a point of reference. Then we could look back to see what had been changed by the vaccine as we go forward,” says coauthor Cosette M. Wheeler, PhD, professor in the Department of Molecular Genetics and Microbiology at the School of Medicine at the University of New Mexico Health Sciences Center in Albuquerque.

Inclusion was limited to Hispanic and non-Hispanic white women because of the insufficient sample size of some other groups and because follow-up studies will include analyses of immunogenetic risk factors that are currently not feasible in other racial/ethnic groups. The cases included in the study were 1,213 women with in situ cervical cancer who were diagnosed between 1985 and 1999 and 808 women with invasive cervical cancer who were diagnosed between 1980 and 1999, and for whom archival paraffin–embedded

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tissue was available for analysis. The controls were 4,007 women ages 18 to 40 years who underwent routine cervical screening from 1996 through 2000 and had portions of their cellular samples frozen in transport medium. The presence and genotype of HPV in samples from cases and controls were determined by polymerase chain reaction–based methods. The relative risks for cervical cancer were calculated, and investigators assessed the factors linked with age at diagnosis and the prevalence of HPV genotypes.

In invasive cancers, the most common HPV type found was HPV–16 (53.2%); other types included HPV–18 (13.1%) and HPV–45 (6.1%). In situ cancers most frequently contained DNA from HPV–16 (56.3%), HPV–31 (12.6%), and HPV–33 (8.0%).

Women whose invasive cancers were positive for other carcinogenic HPV types (not types 16 or 18) were diagnosed at a mean age of 52.3 years (95% confidence interval [95% CI], 50.0–54.6 years), whereas those with invasive cancer who were positive for HPV–16 or HPV–18 were significantly younger at the time of diagnosis: 48.1 years (95% CI, 46.6–49.6 years) and 45.9 years (95% CI, 42.9–49.0 years), respectively.

“It is clear that HPV–16–related cancers occur at a younger age than other cervical cancers,” Dr. Wheeler says. “HPV–16 and –18 are more carcinogenic than other HPV types. They do their job faster,” she says.

“We know based on observation that few cervical cancers occur in women aged younger than 25 years in unvaccinated populations,” Dr. Wheeler says. In fact, the rate is approximately 2 in 100,000. As Dr. Wheeler and her colleagues noted in their discussion, the HPV vaccine could reduce that rate by 50%, a rate similar to that for vaginal cancer, a malignancy for which no screening is conducted. “This could allow us to raise the age of screening for cervical cancer, as other countries have done,” she said. Screening currently begins at age 21 years, or within 3 years of the onset of sexual activity. In the United Kingdom, in contrast, screening typically begins at age 25 years; in the Netherlands, most women are screened starting at age 30 years.

Dr. Wheeler also stresses the importance of putting a clear message out for patients: the current HPV vaccine does not protect against all carcinogenic viruses. “Regardless of a woman’s vaccine status, she must get screened,” she says.

“This study provides baseline data that will be helpful for monitoring the impact of vaccination,” says Debbie Saslow, PhD, director of Breast and Gynecologic Cancer at the American Cancer Society in Atlanta. She points out that other data, mostly taken from modeling studies, support the recommendation that the onset of screening can be safely delayed for women who have received the HPV vaccine. The data from this study confirm that HPV–16 and HPV–18 are associated with cervical cancers at a younger age, which provides reassurance about delayed screening after vaccination, Dr. Saslow says.

“The American Cancer Society and other groups are poised to develop screening recommendations for vaccinated women once data—not just baseline, but monitoring data including that from the vaccine clinical trials—are available,” Dr. Saslow says. “For the time being, however, there is agreement that vaccinated women should follow the same guideline as unvaccinated women because the vaccine has only been available for 2 years and is only effective in women who have not been previously exposed to HPV–16 and –18. Because exposure is very common within the first few years of the onset of sexual activity, we would only recommend delayed onset of screening in girls who were vaccinated as young adolescents. And those girls have not yet reached the earliest age to begin screening,” Dr. Saslow explains.

An editorial by Lauri E. Markowitz, MD, and colleagues from the Centers for Disease Control and Prevention in Atlanta (J Natl Cancer Inst. 2009;101:439 – 440) notes that, “…screening recommendations have been debated even without considering HPV vaccine issues. Guidelines from national organizations promote the initiation of screening at age 21 years or 3 years after the onset of vaginal sex and recommend lengthening of the screening intervals; however, most providers still screen women annually starting at age 18 years or below. Clearly, more education and policy interventions are required to translate evolving guidelines into best public health practice.”

For additional information, see the American Cancer Society screening guidelines for the early detection of cervical neoplasia and cancer at: http://caonline.amcancersoc.org/cgi/content/full/52/6/342 and those regarding the use of the HPV vaccine at: http://caonline.amcancersoc.org/cgi/content/full/57/1/7

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