Highlights from the 2012 Annual Meeting of the American Society of Clinical Oncology

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TREATMENT-RELATED SIDE EFFECTS

Vitamin D Eases Aromatase Inhibitor-Related Arthralgia

Major Finding: At 6 months, 37% of women receiving 30,000 IU vitamin D weekly experienced a per-protocol musculoskeletal event vs. 51% on placebo (P value = .069).
Data Source: Researchers conducted a double-blind, randomized trial of 160 women with stage I-III breast cancer and a vitamin D level of 40 ng/mL or less.
Presenting Author: Qamar J.Khan, University of Kansas Medical Center, Kansas City, KS
Disclosures: Dr. Khan reports honoraria from Abraxis BioScience and Genentech, and research funding from Abraxis and Novartis Roche/Genentech. His coauthors and Dr. Mustian report no disclosures.

BY PATRICE WENDLING
Elsevier Global Medical News

Vitamin D3 can relieve the aches and pains associated with aromatase inhibitor therapy for breast cancer, according to the results of a randomized, double-blind, placebo-controlled trial.

Six months of vitamin D at 30,000 IU per week proved safe and was associated with "less worsening" of musculoskeletal events and fewer overall adverse quality of life events in women starting adjuvant letrozole (Femara) for hormone receptor-positive breast cancer, Dr. Qamar J. Khan reported at the annual meeting of the American Society of Clinical Oncology.

Aromatase inhibitors are often discontinued prematurely because of new or worsening musculoskeletal pain reported in as many as half of women and fatigue in 15%-30%, said Dr. Khan of the University of Kansas Medical Center in Kansas City.

Vitamin D deficiency is thought to contribute to musculoskeletal symptoms, he said, explaining the rationale for the study. It is prevalent in breast cancer patients who have these aches and pains, and in women receiving adjuvant chemotherapy, even with supplementation. A similar syndrome is seen in people with severe vitamin D deficiency, he noted.

A prior pilot study conducted by the investigators suggested that vitamin D at 50,000 IU/wk for 12 weeks may be effective in reducing these symptoms (Breast Cancer Res. 2010;119:111-8).

The current double-blind VITAL (Vitamin D for Arthralgias From Letrozole) trial evenly randomized 160 postmenopausal women with stage I-III hormone receptor-positive invasive breast cancer and a serum vitamin D level of 40 ng/mL or less. All patients received letrozole 2.5 mg daily and the standard daily recommended daily allowance (RDA) of vitamin D 600 IU and calcium 1,200 mg. One cohort also received 30,000 IU of oral vitamin D3 weekly for 24 weeks; the other was given a placebo.

The two arms were well matched with regard to age, race, body mass index, vitamin D level at baseline, adjuvant chemotherapy, and radiation therapy.

The per-protocol primary end point was the incidence of a musculoskeletal event, defined as worsening of pain using a simple pain intensity scale, worsening disability from musculoskeletal pain using the Health Assessment Questionnaire II, or discontinuation of letrozole because of pain at 6 months. The primary end point also was measured, substituting the quantitative Brief Pain Inventory for the simple pain intensity scale, Dr. Khan said.

Thirteen patients did not complete the study for reasons unrelated to study agents and/or musculoskeletal events, leaving 147 evaluable for efficacy.

At 6 months, 37% of women receiving 30,000 IU vitamin D weekly experienced a per-protocol musculoskeletal event, compared with 51% on placebo (P = .069), based on the simple scale. When the more robust Brief Pain Inventory was used, 61% of controls and 38% of those on vitamin D reported a musculoskeletal event, a difference that reached statistical significance (P = .008), he said.

A significantly higher proportion of women on placebo also had an adverse quality of life event, defined as a musculoskeletal event plus worsening of fatigue (72% vs. 42%; P less than .001).

The median vitamin D level at baseline was 25.1 ng/mL in the control arm and 22.5 ng/mL in the vitamin D group. It hovered at 32 ng/mL at 12 weeks and 31 ng/mL at 24 weeks in the control group, but rose to 53 ng/mL at 12 weeks and 57 ng/mL at 24 weeks in the vitamin D arm (P = .001 at both 12 and 24 weeks).

Baseline levels had little influence on the final level achieved. The sharp rise followed by relatively little gain in the active treatment arm suggests a plateau in the effect of continued vitamin D supplementation, Dr. Khan observed.

One patient in the control arm developed mild hypercalcemia, and three patients in the control arm discontinued early because of a musculoskeletal adverse event. There were no severe adverse events.

Discussant Karen Mustian, Ph.D., of the University of Rochester (N.Y.) Medical Center, said that the trial used well-validat-

ed measures and showed no discernable toxicity with 30,000 IU weekly, which is beyond the current RDA. "Therefore it may be promising for helping with these musculoskeletal symptoms and possibly fatigue," she said.

Dr. Mustian asked whether the time needed to achieve a benefit poses a potential problem in terms of patient adherence and whether data are available on the sustainability of the improvements in musculoskeletal symptoms and fatigue.

Dr. Khan said that aromatase inhibitor-induced adverse events tend to peak at about 6 months and that only one study has looked at using higher doses of vitamin D beyond 6 months. The observation that the effect of vitamin D supplementation plateaus at 3-6 months, however, is consistent with other studies.

"After you load the body with vitamin D and … you keep on giving the same dose, the body just maintains the levels," he said.

Dr. Khan said that additional studies are needed to address long-term sustainability, and that the investigators have proposed a trial to the Southwest Oncology Group for the same intervention for 1-2 years to study a longer-term effect.

Dr. Khan reports honoraria from Abraxis BioScience and Genentech, and research funding from Abraxis and Novartis Roche/Genentech. His coauthors and Dr. Mustian report no disclosures.

Olanzapine Overcomes Chemotherapy-Induced Vomiting and Nausea

Major Finding: Seventy-one percent of patients who received olanzapine had no emesis following breakthrough chemotherapy-induced nausea and vomiting, compared with 32% of patients who received metoclopramide (P less than .01) during a 72-hour observation period.

Data Source: These findings come from a double-blind, phase-III study of 80 patients with breakthrough emesis or nausea despite guideline-directed prophylaxis for highly emetogenic chemotherapy.

Presenting Author: Rudolph M. Navari, Indiana University School of Medicine South Bend, South Bend, IN

Disclosures: The authors reported that they have nothing to disclose.

BY KERRI WACHTER

Elsevier Global Medical News

The antipsychotic olanzapine trounced standard therapy for breakthrough chemotherapy-induced nausea and vomiting in a clinical trial that could change the way some cancer patients are treated.

In the double-blind phase III study, 30 (71%) of 42 patients, who received olanzapine (Zyprexa) had no emesis, compared with 12 (32%) of 38 patients who received metoclopramide (P less than .01) during a 72-hour observation period after highly emetic chemotherapy.

In addition, 28 (67%) patients on olanzapine had no nausea, compared with 9 (24%) of those patients on metoclopramide (P less than .01), said Dr. Rudolph M. Navari, who presented the study during a press briefing in advance of the annual meeting of American Society of Clinical Oncology, June 1-5, in Chicago. Dr. Navari is the director of the Harper Cancer Institute at Indiana University in South Bend.

ASCO president-elect Dr. Sandra M. Swain, medical director of the Cancer Institute at Washington Hospital Center, called the findings "a great step forward for quality of life for our patients.

"This is a huge advance," said Dr. Swain, a breast cancer expert, who comoderated the teleconference. "We've come a long way to really treat and cure these patients … these side effects can be intolerable to patients. Sometimes patients will opt out of curative treatment, and we certainly don't want that, when we know we've made advances."

The researchers included chemotherapy-naive patients who received highly emetogenic chemotherapy: more than 70 mg/m2 cisplatin, or more than 50 mg/m2 doxorubicin and more than 600 mg/m2 cyclophosphamide.

Patients who developed breakthrough emesis or nausea despite guideline-directed prophylaxis were randomized to receive olanzapine or metoclopramide. Pre-chemotherapy prophylaxis included intravenous dexamethasone (12 mg), intravenous palonosetron (0.25 mg), and intravenous fosaprepitant (150 mg); post-chemotherapy prophylaxis was daily oral dexamethasone (8 mg, days 2-4).

Patients received 10 mg oral olanzapine for 3 days or 10 mg oral metoclopramide three times daily for 3 days. Patients were monitored for emesis and nausea for the 72 hours after the initiation of therapy. In addition, nausea was measured by patients on a visual analog scale (0-10), with 0 being no nausea and 10 being maximal nausea.

Patients in the two groups were similar for age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, and diagnosis (5 bladder cancers, 40 breast cancers, 8 lymphomas, and 27 lung cancers).

"Both olanzapine and metoclopramide were well tolerated with no grade 3 or 4 toxicities," said Dr. Navari. No central nervous system toxicities were observed in either group.

Olanzapine is indicated for treatment of psychosis and is associated with weight gain, but the side effect should not be a problem for cancer patients.

"The side effect of weight gain occurs in patients, who receive the drug for 3 to 6 to 9 months," Dr. Ravari noted. "So using it for a short period of 3-4 days once a month - we did not see that in the current study, nor did we see that in previous studies."

Dr. Navari had previously reported that patients receiving highly emetogenic chemotherapy were about twice as likely not to experience any delayed nausea with an olanzapine regimen compared with a standard aprepitant (Emend) regimen (68% vs. 37%) in a phase III clinical trial. The two regimens worked similarly well for preventing acute nausea and for preventing both acute and delayed vomiting, that study found (Support. Oncol. 2011;9:188-95).

ASCO presented a preview of some meeting highlights with many of the abstracts being posted online as of 6:00 p.m. Eastern at www.asco.org.

The authors reported that they have nothing to disclose.

Duloxetine Eases Pain of Chemo-Induced Neuropathy

Major Finding: A pain reduction of 30% or more was seen in 33% of patients on duloxetine vs. 17% on placebo.

Data Source: Investigators conducted a double-blind, phase III randomized controlled trial in 231 patients with peripheral neuropathy.

Presenting Author: Ellen M. Lavoie Smith, University of Michigan, Ann Arbor, MI

Disclosures: CALBG 170601 was supported by the National Cancer Institute division of cancer prevention and Lilly Pharmaceuticals. Dr. Smith reported no conflicts of interest. A coauthor reported research funding from Merck.

BY PATRICE WENDLING
Elsevier Global Medical News

The antidepressant duloxetine reduces chronic pain from chemotherapy-induced peripheral neuropathy with fewer side effects than with current therapies, according to results of a phase III, double-blind trial.

Among evaluable patients, 59% reported less pain with duloxetine (Cymbalta), compared with 38% with placebo. A pain reduction of 30% or more - a measure considered clinically significant - was reported by 33% and 17%, respectively.

"Duloxetine 60 mg a day is the first drug to be shown to be effective in painful chemotherapy-induced peripheral neuropathy based on the results of a randomized trial," Ellen Lavoie Smith, Ph.D., said at a press conference at the annual meeting of the American Society of Clinical Oncology.

A variety of other agents - including gabapentin and tricyclic antidepressants - have been shown to be effective in treating neuropathic pain and are routinely pressed into service in oncology practice, but have failed to demonstrate efficacy in randomized trials of peripheral neuropathy caused by chemotherapy, she noted.

"Some patients endure this painful neuropathy for months and possibly for as long as years following completion of chemotherapy," she said. "It's chronic, it's very distressing and it's disabling. And there is nothing to date effective in treating this problem."

Duloxetine is approved to treat major depressive disorder, with an additional indication for chronic musculoskeletal pain added in 2010. The safety label was revised in September 2011 to include warnings for severe skin reactions including Stevens-Johnson Syndrome and erythema multiforme.

The Cancer and Leukemia Group B (CALGB) 170601 trial randomized 231 patients with painful neuropathy after receiving single-agent paclitaxel (Taxol) or oxaliplatin (Eloxatin) chemotherapy to duloxetine 30 mg for 1 week and 60 mg for 4 weeks, followed by crossover to placebo after a 1-week washout period or the same regimen in the opposite order. Pain levels were assessed weekly using the Brief Pain Inventory-Short Form (BPI-SF) in 220 patients.

The average change in BPI-SF score, the study's primary outcome, was -1.09 in patients given duloxetine, compared with -0.33 given placebo (P = .003), reported Dr. Smith, with the University of Michigan, Ann Arbor.

During duloxetine treatment, patients also experienced a significant reduction in the BPI-SF pain interference score, a sum of seven items including interference with general activity, mood, walking, normal work, relations with people, sleep and enjoyment of life. There was no difference in duloxetine efficacy based on the specific neurotoxic chemotherapeutic agent received.

In all, 21% of patients said their pain was cut by at least one-half with duloxetine, while only 9% taking placebo did.

Interestingly, 11% of patients saw their pain increase with the serotonin-norepinephrine reuptake inhibitor, compared with 28% with placebo. The reason for the finding is unclear, Dr. Smith said in an interview.

"Pain is a very complicated thing to study," she said. "There are many things that go into it - psychosocial issues, environmental issues, cultural issues, but again, there may be patients who are more likely to respond to these drugs because their central nervous system isn't really working normally."

Overall, duloxetine was well tolerated, but was associated with significantly more grade 2 or greater fatigue than placebo (11% vs. 3%; P = .029). Dr. Smith pointed out that the overall incidence of side effects was lower than observed in two studies of diabetes-related peripheral neuropathy, likely because they used the 60 mg-dose without the lower 30 mg starting dose.

Dr. Hope Rugo, an oncologist at the University of California, San Francisco, and an associate editor for The Oncology Report, who was not involved in the study, said one of the advantages of duloxetine is the lack of somnolence observed in the study - a side effect that is bothersome to many of her breast cancer patients taking gabapentin for chronic neuropathic pain induced by taxanes or platinum-based therapy.

Press briefing moderator Dr. Nicholas Vogelzang, head of genitourinary cancer at the Nevada Cancer Institute in Las Vegas, echoed those remarks and said that neuropathy is fairly common among his patients treated with platinum-based chemotherapy. Duloxetine is an addition to the oncologist's armamentarium, he said, adding "I'm certainly going to use this when I get back to the office."

Dr. Smith acknowledged that not everyone responded to duloxetine, but said that the dual serotonin norepinephrine reuptake inhibitor improves compliance with chemotherapy treatment and that most patients saw improved function and quality of life.

Patients with depression were excluded from the trial, so the effect of duloxetine was not simply because of improved mood, she said. Instead, it is thought that the drug eases pain by increasing serotonin and norepinephrine, and that responders may have an abnormality in the way their brain processes pain because of lower levels of these two pain-inhibiting neurotransmitters. Future work will try to determine which patients are most likely to respond to the antidepressant.

CALBG 170601 was supported by the National Cancer Institute division of cancer prevention and Lilly Pharmaceuticals. Dr. Smith reported no conflicts of interest. A coauthor reported research funding from Merck. Dr. Rugo has received research funding from Genentech/Roche, Abraxis BioScience, and Bristol-Myers Squibb.

Chemotherapy-Induced Neuropathy Linked to Falls

Major Finding: About 12% of patients with chemotherapy-induced peripheral neuropathy had at least one fall, and nearly 60% experienced some kind of physical problem related to CIPN.

Data Source: This was an analysis of baseline assessments from a phase III randomized trial.

Presenting Author: Supriya Gupta Mohile, University of Rochester Medical Center, Rochester, NY

Disclosures: The study was funded by grants from the National Cancer Institute. Dr. Mohile reported no relevant disclosures. Dr. Loprinzi disclosed receiving research funding from Abbott, Amgen, Bristol-Myers Squibb, Eisai, Novartis, Ortho Biotech, Pfizer, Roche, and Sanofi.

BY NEIL OSTERWEIL
Elsevier Global Medical News

Cancer survivors with chemotherapy-induced peripheral neuropathy may be headed for a fall, researchers cautioned at the annual meeting of the American Society of Clinical Oncology.

About 12% of patients with chemotherapy-induced peripheral neuropathy (CIPN) had at least one fall, and nearly 60% experienced some kind of physical problem related to CIPN, reported Dr. Supriya Mohile of the department of hematology/oncology at the University of Rochester (N.Y.).

"We should in our clinics longitudinally evaluate patients not only for toxicities from neuropathy, but also for physical functioning and falls," she said.

Dr. Mohile urged providing patients with balance and mobility training throughout chemotherapy and minimizing fall risk by recommending assistive devices and home-safety evaluations and modifications as necessary.

She and her colleagues evaluated 421 patients who had reported baseline data as part of a randomized phase III trial for a topical cream. The patients had completed chemotherapy and had self-reported CIPN of 4 or greater on an 11-point scale. The patients were not on significant medications for either pain or neuropathy, and those with other possible causes of neuropathy, such as diabetes, were excluded.

They found that about one-third of patients had a CIPN-related problem such as difficulty stooping, walking for one-fourth of a mile, or performing tasks requiring heavy lifting.

Additionally, more than 25% reported a functional loss, limiting their ability to shop, manage money, walk across a room, do light housework, or bathe themselves.

Comparing 260 patients who reported falls or physical problems with 161 who did not, the investigators identified pain, sensory neuropathy, and motor neuropathy as toxicities independently associated with falls and/or physical problems (P less than .001 for all three comparisons).

In a multivariate analysis controlling for age, sex, race, ethnicity, marital status, education, history of taxane exposure, previous surgery and radiation, pain, and sensory neuropathy, the investigators found that breast cancer (odds ratio, 2.776; P = .045) and motor neuropathy (OR, 1.138; P = .006) were independently associated with falls. Factors associated with having a physical performance problem were previous surgery (OR, 2.536; P = .013) and motor neuropathy (OR, 1.325; P less than .001).

Functional losses were more likely to occur among Hispanics (OR, 5.318; P = -.048), patients with any physical performance problem (OR, 4.942; P less than .001), and those with motor neuropathy (OR, 1.191; P = .0001).

The study was limited by the heterogeneity of the cancer sample, its cross-sectional design that precludes determination of causality or of a temporal relationship between chemotherapy and neuropathies, and self-report of CIPN toxicities, Dr. Mohile said.

Commenting on the study, Dr. Charles L. Loprinzi, emeritus chair of the division of medical oncology at the Mayo Clinic in Rochester, Minn., said that it supports earlier findings of a relationship between epidermal nerve fiber loss and deficits in sensory and motor function leading, and that "it makes sense" that such losses would lead to functional losses.

The study was funded by grants from the National Cancer Institute. Dr. Mohile reported no relevant disclosures. Dr. Loprinzi disclosed receiving research funding from Abbott, Amgen, Bristol-Myers Squibb, Eisai, Novartis, Ortho Biotech, Pfizer, Roche, and Sanofi.

Studies Clash on Cardiac Effects of TKIs in Kidney Cancer

Major Finding: Whereas LVEF declines of 16% or greater from baseline were seen in 1.8%-2.3% of kidney cancer patients treated with sunitinib or sorafenib in a randomized trial, most patients on targeted therapies, including sunitinib and sorafenib, developed cardiovascular toxicities, including hypertension, in a single-center study.

Data Source: Investigators from the ECOG E2805 trial and Stanford University presented prospective and retrospective findings, respectively.

Presenting Authors: Naomi B. Haas, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA; Philip S. Hall, Stanford University, Internal Medicine Residency Program, Palo Alto, CA.

Disclosures: The ECOG E2805 trial was supported by the National Cancer Institute. Dr. Haas reported having a consulting or advisory role to Boehringer Ingelheim, Dendreon, Novartis, and Pfizer, and receiving research funding from GlaxoSmithKline. Dr. Hall reported having no relevant disclosures. Dr. Eisen has received honoraria and serves in a consulting or advisory role to Astellas and AVEO.

BY NEIL OSTERWEIL
IMNG Medical News

Take your pick: The tyrosine kinase inhibitors sunitinib and sorafenib do/do not appear to have significant cardiac toxicity when used in adjuvant therapy for renal cell carcinoma.

Conflicting studies presented at the meeting suggest that - for now at least - it's a toss-up.

A cardiac substudy of the phase III ECOG (Eastern Cooperative Oncology Group) E2805 ASSURE (Adjuvant Sunitinib or Sorafenib for Unfavorable Renal Carcinoma) trial, comparing either sunitinib (Sutent) or sorafenib (Nexavar) with placebo in patients with resected renal cell carcinoma (RCC), showed that neither TKI was associated with significant declines in left ventricular ejection fraction (LVEF) or other cardiac adverse events when compared with placebo, said Dr. Naomi B. Haas of the University of Pennsylvania, Philadelphia.

Left ventricular dysfunction that did occur with the TKIs was reversible, and ischemic events were uncommon and not clearly linked to therapy, she added.

"The implications for patients: Further prospective study on the effects of these agents is needed in patients who have preexisting cardiac dysfunction. This was a well population we were looking at," said Dr. Haas.

However, a retrospective study by Dr. Phillip S. Hall and colleagues at Stanford (Calif.) University found evidence of significant cardiac toxicity in patients with metastatic renal cell carcinoma that was treated with both agents and with other targeted therapies at their institution.

"Cardiovascular toxicity is an important adverse event related to targeted-therapy administration. Close monitoring for the development of CV toxicity with the use of these agents should become standard of care, as early detection of asymptomatic patients could preempt symptomatic toxicity and reduce treatment-related morbidity and mortality," they wrote in a poster presentation.

TKIs on Trial

Previous studies, most of them retrospective, have reported cardiac dysfunction with TKI use ranging from 1% to 28%. The proposed mechanism of action is through the metabolic dysfunction of cardiac myocytes, Dr. Haas said.

She and her coinvestigators in the ECOG E2805 ASSURE trial looked at data from a cardiac substudy, and asked whether either sorafenib or sunitinib was associated with a decline in LVEF, clinically significant heart failure (HF) or other effects, using multigated acquisition scans (MUGA) at baseline and at 3, 6, and 12 months (study end) or at the end of treatment.

There were nine cases of the primary end point (a decline in LVEF of 16% or greater from baseline) among 397 patients on sunitinib, seven among 394 patients on sorafenib, and five among 502 patients on placebo. The respective event rates were 2.3%, 1.8%, and 1.0%; these differences were not clinically significant.

The numbers for other cardiac events - including LVEF decline of 16% or more below the institutional level of normal occurring after 6 months, or a grade 2 or 3 left ventricular systolic or diastolic dysfunction - were also similar among the groups, occurring in 12, 11, and 11 patients, respectively.

"Looking at the data as they stand, it on the face of it is very reassuring, with the primary end point being met in a very small proportion of patients," commented the invited discussant Dr. Tim Eisen, professor of oncology at the University of Cambridge (England).

He pointed out, however, that new cardiac events were seen in the study past 6 months of therapy, which indicated that investigators should continue to monitor patients for cardiotoxicities throughout the course of therapy and in follow-up.

TKIs in Practice

The Stanford investigators looked at the incidence of hypertension, left ventricular dysfunction, changes in serum markers of cardiovascular toxicity, and heart failure in 159 patients with metastatic RCC who were treated from 2004 through 2011. They found that 116 of 159 patients (73%) developed cardiovascular toxicities.

"Sunitinib was the most frequently used and most common offending agent, with 66 of 101 sunitinib-treated patients (65%) developing a form of CV toxicity, or 32 of 101 (32%) excluding hypertension. However, it was notable that CV toxicity was observed in 68%, 66%, and 51% of patients treated with bevacizumab, sorafenib, and pazopanib as well," the investigators wrote.

They noted that there were fewer toxicities with mTOR (mammalian target of rapamycin) inhibitors than with TKIs, but the sample sizes were small.

The ECOG E2805 trial was supported by the National Cancer Institute. The Stanford study was internally funded. Dr. Haas reported having a consulting or advisory role to Boehringer Ingelheim, Dendreon, Novartis, and Pfizer, and receiving research funding from GlaxoSmithKline. Dr. Hall reported having no relevant disclosures. Dr. Eisen has received honoraria and serves in a consulting or advisory role to Astellas and AVEO.

Scalp Cooling Protects Against Chemotherapy-Induced Alopecia

Major Finding: Of women who used scalp-cooling headgear, 24% did not wear a wig or headband upon completion of chemotherapy, compared with 4% of a control group.

Data Source: Investigators conducted a cohort study in 110 patients who tried scalp cooling during breast cancer chemotherapy and 26 women who did not have access to a scalp-cooling device.

Presenting Author: Julie Lemieux, URESP, Centre de Recherche FRSQ du CHA Universitaire de Québec, Quebec City, QC, Canada

Disclosures: The trial was funded by the Fondations des Hôpitaux Enfant-Jésus et Saint-Sacrement, the Canadian Breast Cancer Research Alliance, and Sanofi-Aventis. Dr. Lemieux received a research grant from the Fonds de la Recherche en Santé du Québec.

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

Wearing a scalp-cooling cap can reduce hair loss in women receiving chemotherapy for breast cancer, the results of a small prospective cohort study suggest.

Among women who used the cooling headgear starting 20 minutes before chemotherapy and continuing for 60-90 minutes after the infusion, 24% did not wear a wig or headband upon completion of chemotherapy, compared with 4% of a control group that did not have access to the device, investigators reported.

Further, patient satisfaction scores were higher than these numbers in a blinded assessment, according to Dr. Julie Lemieux of Laval University in Quebec City and her coinvestigators. To grade the results with and without the cooling device, a hairdresser looked at before and after photos of women in the study, and was not told which women were in the scalp-cooling group. The criteria for successful hair preservation was characterization of hair loss as "not at all," "a little," or "moderate" from the beginning to the end of chemotherapy. The procedure was deemed a failure if the reviewer rated hair loss as "a lot," or "all," or "hair shaved."

The hairdresser graded the hair loss intervention as successful in 34% of the scalp-cooling group - as did 49% of the women who wore the caps. Only 9% of the control group received a successful grade from the hairdresser; even fewer, 4%, agreed they had not had substantial hair loss.

In all, 69% of women who tried scalp cooling said the advantages outweighed the disadvantages, and 78% said they would recommend it to other women receiving the same chemotherapy for breast cancer.

"When you look at patient evaluations, they are … more optimistic than the hairdresser evaluations. They were more satisfied," Dr. Lemieux said in a poster-side interview at the meeting, where she displayed the results.

Scalp-cooling systems are approved for the reduction of alopecia in Canada, she said, but controversy persists among oncologists over safety and impact, if any, on the effectiveness of chemotherapy.

"If you cool the scalp there is vasoconstriction, so there is less blood that goes in the scalp ... that is the main mechanism," Dr. Lemieux explained. One concern is that scalp metastases could increase; another is that patients might receive less chemotherapy as a result.

Dr. Lemieux and her colleagues reviewed seven randomized trials of hair-cooling studies and found no safety signals. In all, 260 women were enrolled, and the studies covered a variety of chemotherapy regimens, including at least one that is not known to cause alopecia.

They also did a retrospective cohort study, and found that the incidence of scalp metastases was about 1% whether women used scalp cooling or not (Breast Cancer Res. Treat. 2009;118:547-52). Subsequently, they reported on two cases where the scalp was the first metastatic site, with metastases occurring 7 and 9 years after cooling (Breast Cancer Res. Treat. 2011;128:563-6).

At the San Antonio Breast Cancer Symposium, Dr. Lemieux and her associates reported on a retrospective study that found no difference in survival between patients who used scalp cooling and those who did not.

The system tested in the study used a cap that is placed in a freezer and changed every 20-30 minutes, starting 20 minutes before chemotherapy and continuing for 60-90 minutes afterward. A new generation of scalp-cooling systems uses a compressor that circulates cold fluid in the cap, and it does not have to be changed.

Dr. Lemieux said the researchers conceived the study as a pilot for a larger randomized controlled trial that will address efficacy, cost, and quality of life issues. They are seeking to raise funds, as the companies that make the systems are too small to sponsor a large trial.

Cost is a concern, she noted, because of the additional time the women spend in the infusion room. "So you have to have that time available in the chemotherapy room," she said. "We also want to look at the cost of the system, of the extra time that women are in hospital, and at quality of life, too.

Vemurafenib Soon After Ipilimumab Linked With Rash

Major Finding: Four patients (25%) developed grade 3 maculopapular skin rash that histologically had features of a drug hypersensitivity rash.

Data Source: A single-center retrospective case series of 16 patients with BRAFV600E-mutant metastatic melanoma treated with vemurafenib after ipilimumab

Presenting Author: James J. Harding, Memorial Sloan-Kettering Cancer Center, New York, NY

Disclosures: Dr. Harding disclosed no relevant conflicts of interest. Dr. Sznol disclosed that he is a consultant to Abbott Laboratories, Anaeropharma Science, BioVex, Bristol-Myers Squibb, Genesis Biopharma, Genzyme, and Prometheus; receives honoraria from Prometheus; and receives research funding from Bristol-Myers Squibb.

BY SUSAN LONDON
IMNG Medical News

The sequencing and timing of two new targeted therapies for melanoma may have important implications for the development of serious skin toxicity, according to one center's experience.

Investigators at Memorial Sloan-Kettering Cancer Center in New York retrospectively identified 16 patients treated there for BRAFV600E-mutant metastatic melanoma who received vemurafenib (Zelboraf) after ipilimumab (Yervoy).

Vemurafenib is an inhibitor of the BRAF kinase. Ipilimumab blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA 4), which normally acts as a key checkpoint or brake in the immune system.

Four of the patients (25%) developed a grade 3 maculopapular rash, according to data reported in a poster session at the annual meeting of the American Society of Clinical Oncology.

Biopsy findings suggested these were drug hypersensitivity reactions, and analyses showed that grade 3 rash was much more likely when vemurafenib was given within 1 month of stopping ipilimumab as compared with later (100% vs. 8%, P = .007).

"It's interesting to speculate that loss of checkpoint inhibition by ipilimumab might predispose patients to drug reactions," lead investigator Dr. James J. Harding commented in an interview, while cautioning that the study was very small and retrospective.

"The take-home message is these agents, both of which improve overall survival, will be used in sequence. It's not clear if there is a benefit of sequencing one before the other or combin-

ing them - that will be studied prospectively," he noted, as in the case of an ongoing phase I-II trial looking at the two drugs together (NCT01400451).

"Until more data are available, it's possible that there may be a significant maculopapular rash if you give vemurafenib within a month of ipilimumab. In almost all cases, a dose interruption followed by dose reduction is acceptable," he added.

"One thing that people need to remember is that if you give vemurafenib after ipilimumab, you are giving a combination therapy because the ipilimumab half-life is 2 weeks," noted discussant Dr. Mario Sznol, vice-chief of medical oncology with the Yale Medical Group in New Haven, CT.

"I would have hoped that we would have seen really dramatic antitumor effects with this combination, especially in the patients who were treated soon after their last dose of ipilimumab. And in fact that's not what we saw," he added. "I don't think this curve [waterfall plot] looks much better than what we would have seen with vemurafenib alone in this population of patients," with no apparent difference for patients receiving vemurafenib within 45 days of ipilimumab and the rest.

"So it's just a warning that there will be sequence issues and toxicity interactions, and we really need to know the biology when we combine these agents," Dr. Sznol concluded. "We may do better with this combination, but we may not. We may need to use this in combination with other agents."

Of the 16 patients studied, 13 (81%) developed any-grade skin rash on vemurafenib, making this by far the most common adverse event observed. (For comparison, the rate of skin rash with vemurafenib was 37% in the BRIM-3 trial and 52% in the BRIM-2 trial.)

The cases of grade 3 rash developed within 6-8 days of starting vemurafenib and began as a pruritic eruption on the neck or chest that rapidly expanded to involve the back, trunk, and extremities. The incidence seen was triple that in the BRIM-3 trial (25% vs. 8%, P = .02).

Biopsies, performed in two of the four patients, revealed spongiotic and perivascular dermatitis with eosinophils, consistent with drug hypersensitivity reaction.

Although the time elapsed since the prior ipilimumab influenced the development of grade 3 rash, the dose of prior ipilimumab, number of doses, and immune-related adverse events did not.

None of the rashes progressed to anaphylaxis or Stevens-Johnson syndrome. Steroids appeared to be largely ineffective, according to Dr. Harding; one patient developed the rash while already taking steroids, and another was given steroids with little to no improvement.

"We essentially stopped the vemurafenib and then redosed it 11 days later [after the rash resolved]. And, with the exception of one patient, all of the patients tolerated it well and were able to continue," he reported.

The objective overall response rate with vemurafenib was 50%, similar to what was seen in the prior phase II and III trials of the drug.

Dr. Harding disclosed no relevant conflicts of interest. Dr. Sznol disclosed that he is a consultant to Abbott Laboratories, Anaeropharma, BioVex, Bristol-Myers Squibb, Genesis Biopharma, Genzyme, and Prometheus; receives honoraria from Prometheus; and receives research funding from Bristol-Myers Squibb.

Acetyl-l-Carnitine Yields Mixed Results for Chemo-Induced Neuropathy

Major Finding: Patients taking ALC for prevention were more likely to have a greater than 5-point worsening of FACT-NTX score (38% vs. 28%), whereas patients taking ALC for treatment were more likely to have an improvement of at least one grade in neuropathy (51% vs. 24%).

Data Source: Investigators presented separate, randomized, placebo-controlled phase III trials among 410 women receiving adjuvant taxane chemotherapy for breast cancer and 239 patients with cancer and chemotherapy-induced peripheral neuropathy.

Presenting Authors: Dawn L. Hershman, Columbia University Medical Center, New York, NY; Yuanjue Sun, Sixth Affiliated Hospital of Shanghai Jiaotong University, Shanghai, China

Disclosures: Dr. Hershman, Dr. Sun, and Dr. Barton disclosed no relevant conflicts of interest; the ZHAOKE-2007L03540 trial was sponsored by Lee's Pharmaceutical Limited.

BY SUSAN LONDON
IMNG Medical News

The impact of acetyl-l-carnitine on chemotherapy-induced peripheral neuropathy may depend largely on the clinical context and patient population, a pair of phase III trials suggests.

Acetyl-l-carnitine (ALC), a natural substance marketed over the counter as a dietary supplement, is popular among cancer patients as a result of preclinical and early-phase data in chemotherapy-related neuropathy and also a study in patients with diabetes-related peripheral neuropathy.

But in a trial among 409 U.S. women receiving adjuvant chemotherapy for breast cancer, those who took ALC not only had no decrease in the development of peripheral neuropathy symptoms relative to peers who were given a placebo, but actually had an increase. And they had a higher rate of serious neuropathy, too.

In contrast, in a trial among more than 200 Chinese patients with various cancers who had peripheral neuropathy from previous chemotherapy, those who took ALC were more likely than those who took a placebo to have an improvement of at least one grade in their neuropathy. They also were more likely to have improvements in fatigue and strength.

Taken together, the two trials, which were reported in a poster discussion session at the meeting, provide yet another cautionary lesson on the complexity of combining conventional and complementary therapies.

"The use of ALC for prevention is not recommended, and I would say, based on [these results], should be cautioned against. It will be interesting to see the carnitine data and to understand, as much as possible, why the trial was negative," commented Debra L. Barton, Ph.D., of the Mayo Clinic in Rochester, Minn., who was invited to discuss the research. "Further studies are needed to really understand if ALC should be used to treat peripheral neuropathy."

ALC for Prevention of Peripheral Neuropathy

In the first trial, Southwest Oncology Group (SWOG) protocol S0715, investigators led by Dr. Dawn L. Hershman randomized women receiving adjuvant taxane chemotherapy for early breast cancer evenly to either oral ALC 1,000 mg three times daily or matching placebo, for 24 weeks.

Compared with their counterparts in the placebo group, women in the ALC group were more likely to have a greater than 5-point adjusted decrease on the neurotoxicity subscale of the Functional Assessment of Cancer Therapy-Taxane (FACT-NTX) instrument at 12 weeks (odds ratio, 1.48; P = .08) and also at 24 weeks (38% vs. 28%; OR, 1.57; P = .05).

This magnitude of worsening is clinically meaningful, maintained Dr. Hershman of Columbia University in New York, "so this is not like a lot of studies where you find a statistically significant difference that's not clinically meaningful."

In addition, the incidence of grade 3/4 neurotoxicity was 3.8% with ALC, much higher than the 0.5% seen with placebo.

Patients in the ALC group also had scores on the FACT trial outcome index subscale (FACT-TOI), an overall measure of function, that were on average 3.5 points lower (worse) than those among their placebo counterparts (P = .03). There were no significant differences between groups in terms of fatigue and other toxicities.

The investigators have collected biosamples and will be assessing potential biological correlates with peripheral neuropathy outcomes, according to Dr. Hershman.

"We are looking at DNA, oxidative stress, and carnitine levels to better understand the mechanisms of chemotherapy-induced peripheral neuropathy to begin with, because there is not a whole lot known in terms of mechanism," she said. "If we can figure out what makes people worse, then we will maybe be able to figure out how to make people better from a more mechanistic standpoint, because there are very few drugs to treat chemotherapy-induced peripheral neuropathy."

An obvious concern from the trial's findings is that ALC may somehow potentiate the neurotoxic effects of taxanes. "Based on these data, physicians should be telling patients not to take ALC during adjuvant chemotherapy," Dr. Hershman concluded. "You need to talk to patients. We know from the literature that overwhelmingly large number of patients take supplements during chemotherapy and afterward, many of which have not been tested. It's important to get that history from patients."

Dr. Barton, the discussant, praised the trial's rigorous methodology and proposed that there may have been several reasons for the lack of ALC benefit in preventing neuropathy, despite compelling earlier data.

Previous prevention research was done in animals and thus may not translate to humans, she said. And a positive trial for treatment in humans used intravenous administration, which may result in different bioavailability. Finally, "ALC capsules needed to be taken three times a day, and they are rather large, and these patients were, after all, on chemotherapy. They were likely nauseated [and] dyspeptic, and taking what some might call a horse pill three times a day could not have been an easy task. The study did use pill diaries, but we know those aren't a perfect tool for adherence."

"The great thing is that the study collected blood and they are able to look at carnitine levels," Dr. Barton said. "So if carnitine is up in the group that got acetyl-carnitine and not in the group that got placebo, well, I think that pretty much confirms that this just didn't work."

ALC for Treatment of Peripheral Neuropathy

In the second trial, protocol ZHAOKE-2007L03540, investigators led by Dr. Yuanjue Sun of the Sixth Affiliated Hospital of Shanghai (China) Jiao Tong University, enrolled 239 patients who had cancer of various types and stages, had completed chemotherapy, and had had at least grade 2 peripheral neuropathy for up to 6 months.

They were randomly assigned to receive either oral ALC at a dose of 3 g/day or matching placebo, for 8 weeks, with outcomes assessed at clinic visits or by telephone.

Analyses showed that compared with their counterparts in the placebo group, patients in the ALC group were more likely to have had an improvement of at least one grade in their neuropathy, both at 8 weeks (51% vs. 24%; P less than .001) and at 12 weeks (58% vs. 40%; P less than .001).

In terms of secondary outcomes, the ALC group was also more likely to have had an improvement in cancer-related fatigue (31% vs. 20%; P = .048), physical strength (29% vs. 13%; P = .02), and electrophysiology in peripheral nerves (75% vs. 58%; P = .02).

The two groups had statistically indistinguishable rates of adverse events (20% vs. 15%) and adverse reactions (6% vs. 5%). The most common events were gastrointestinal ones and skin allergies.

"This is the first time to confirm that ALC has a positive effect to cure chemotherapy-induced peripheral neuropathy in the Chinese population," Dr. Sun commented through a translator.

"I think the very important thing for this trial is, it is a different kind of patient population. Before this, most clinical trials were performed in [whites] or maybe Americans. This is an only-Asian [population]," he noted, and it is possible that there are genetic differences in how ALC is metabolized.

Dr. Barton, the discussant, took a cautionary view, saying that "there are some things to consider before going out and telling patients to consider acetyl-carnitine for their peripheral neuropathy."

It was unclear from the results reported whether the two treatment groups were well balanced and what criteria were used to define improvement for the secondary outcomes, she noted. Additionally, "outcome measures were all provider graded, [and there were] no self-report measures, so it is difficult to understand the impact of treatment on symptoms, particularly from the patient perspective," she noted.

Dr. Hershman, Dr. Sun, and Dr. Barton disclosed no relevant conflicts of interest; the ZHAOKE-2007L03540 trial was sponsored by Lee's Pharmaceutical Limited.

Docs Need Primer on Long-Term Effects of Chemotherapy

Major Finding: Only 6% of primary care physicians were able to identify the main long-term effects of doxorubicin, paclitaxel, oxaliplatin and cyclophosphamide, compared with 65% of oncologists.

Data Source: Survey of 1,072 primary care physicians and 1,130 oncologists.

Presenting Author: Larissa Nekhlyudov, Harvard Medical School and Harvard Vanguard Medical Associates, Boston, MA

Disclosures: The authors reported no disclosures.

BY PATRICE WENDLING
Elsevier Global Medical News

Many primary care physicians - and even some oncologists - are unaware of common long-term side effects of four widely used breast and colorectal cancer drugs, a national survey by the National Cancer Institute reveals.

Only 6% of primary care physicians were able to identify the main long-term effects (LEs) of doxorubicin (Adriamycin), paclitaxel (Taxol), oxaliplatin (Eloxatin), and cyclophosphamide (Cytoxan), compared with 65% of oncologists surveyed.

The results are not surprising, but they underscore the need for ongoing education among all physicians who care for the more than 12 million cancer survivors in the United States, lead author Dr. Larissa Nekhlyudov said during a press briefing highlighting research to be presented at the upcoming annual meeting of the American Society of Clinical Oncology (ASCO).

"These findings emphasize that in the transition of patients from oncology to primary care settings, primary care providers should be informed about the late effects of cancer treatment so that they may be better prepared to recognize and address these among cancer survivors in their care," said Dr. Nekhlyudov, a primary care physician (PCP) with Harvard Medical School in Boston and Harvard Vanguard Medical Associates in Kenmore, Mass. "Whether this will be achieved with survivorship care plans needs to be evaluated."

The "Survey of Physician Attitudes Regarding the Care of Cancer Survivors" was launched by the National Cancer Institute in 2009, with one survey mailed to a nationally representative sample of 1,072 PCPs and the other to 1,130 medical oncologists who only cared for patients with colorectal or breast cancer.

When asked to report the five LEs they had observed and/or had seen reported in the literature for each of the four standard chemotherapy drugs, 95% of oncologists identified cardiac dysfunction as an LE of doxorubicin, compared with 55% of PCPs (P less than .0001), Dr. Nekhlyudov said.

Similarly, peripheral neuropathy was correctly identified as an LE of paclitaxel and of oxaliplatin by 97% of oncologists, but by only 27% and 22%, respectively, of PCPs (both P less than .0001).

The survey suggests, however, that some oncologists could also use additional continuing education. Premature menopause and secondary malignancies - two long-term effects associated with the alkylating agent cyclophosphamide - were identified by only 71% and 62% of oncologists, respectively, along with 15% and 17%, respectively, of PCPs.

Oncologists and PCPs mostly missed pulmonary fibrosis as a late effect for paclitaxel (5% and 6%, respectively; P = .42) or oxaliplatin (5% and. 9%, respectively; P = .0002). They did a little better in pointing out a possible association with cyclophosphamide (20.6% and 13%; P less than .0001), which has been noted in the literature, she observed.

Dr. Nekhlyudov suggested that the lack of awareness among oncologists is likely because much of the focus has been on the treatment of cancer, and only recently have physicians become aware of the importance of survivorship and the potential for late effects.

"While it is surprising that oncologists were not more aware of late effects, I think that as more and more attention is placed on cancer survivorship, oncologists will become more equipped with that information," she said.

ASCO president and press briefing comoderator Dr. Michael Link said the problem of survivorship has long been recognized in pediatric oncology, where patients frequently relocate, outgrow their pediatrician, or even deny they ever had cancer. Groups such as ASCO and the Institute of Medicine, most recently through its "Lost in Transition" report, have offered guidance for improving transitions among survivors, including the provision of a cancer care plan.

"I think the need for all of this has been highlighted in this abstract and certainly, it's a shot across the bow with things that need to be done," he said.

In adjusted analyses, oncologists who were not board certified were less likely to identify the main LEs for all four drugs (odds ratio, 0.58). Oncologists were more likely to know their LEs if they spent 51%-90% of their time on patient care (OR, 1.87) or more than 90% of their time with patients (OR, 1.82). Age, sex, race, U.S. training, type of practice, and percentage of uninsured patients were not associated with LE awareness, Dr. Nekhlyudov said.

Previous results from the survey reported at last year's ASCO annual meeting indicated that PCPs had low confidence in their knowledge of breast and colon cancer survivors, and reported low marks for their skills in caring for these patients. In addition, neither PCPs nor oncologists felt that a PCP-led model was ideal for survivorship care (J. Clin. Oncol. 2011;29[suppl.];abstract CRA9006).

Dr. Nekhlyudov will formally present her study at ASCO at 5:30 p.m. June 2. The abstract can be viewed at www.abstract.asco.org.

The authors reported no disclosures.

Hodgkin's Survivors Face High Breast Cancer Risk

Major Finding: Nearly a third (30%) of females treated with chest radiation for Hodgkin's lymphoma was diagnosed with breast cancer by age 50.

Data Source: Investigators analyzed data on 1,268 childhood cancer survivors in the Childhood Cancer Survivor Study and 4,570 first-degree relatives of breast cancer patients in the Women's Environmental Cancer and Radiation Epidemiology (WECARE) study.

Presenting Author: Chaya S. Moskowitz, Memorial Sloan-Kettering Cancer Center, New York, NY

Disclosures: The investigators had no relevant financial disclosures.

BY JANE SALODOF MACNEIL
Elsevier Global Medical News

Breast cancer risk is much higher than previously recognized among women who received chest radiation for Hodgkin's lymphoma when they were children, investigators reported.

By the time these survivors are 50 years of age, breast cancer incidence is 30% - "remarkably similar" to the 31% incidence observed in the high-risk group of women with BRCA1 mutations, Chaya S. Moskowitz, Ph.D., and her colleagues determined in a study presented at the meeting.

Although the effect was less dramatic, cumulative risk also was elevated in survivors of other childhood cancers treated with chest radiation, reaching 24% overall by age 50, Dr. Moskowitz said at a press briefing. Among the general population of women in the United States, it is 4% at that benchmark, she noted.

Particularly concerning is the heightened risk observed in women who received less radiation than the current threshold at which the Children's Oncology Group (COG) recommends breast cancer surveillance. The COG says that survivors who received 20 Gy or more of chest radiation should start annual mammograms at age 25 years or 8 years after radiotherapy, whichever comes later.

In this group, 12% of survivors will develop breast cancer by age 40, said Dr. Moskowitz, a biostatistician at Memorial Sloan-Kettering Cancer Center in New York. The study showed that breast cancer incidence also was elevated, albeit not as dramatically - 7% by age 40 - among survivors who received 10-19 Gy of radiation.

Excess risk in those treated with 10-19 Gy warrants "consideration of breast cancer surveillance strategies similar to the current recommendations for women treated with [more than] 20 Gy," the investigators concluded.

About 50,000 survivors received 20 Gy or more of radiation and, therefore, meet the current threshold, Dr. Moskowitz said. Lowering the threshold to include survivors who were treated with 10-19 Gy of chest radiation would add another 7,000-9,000 women.

Increasing public awareness is crucial to increasing surveillance. "Many women who were treated with chest radiation don't know they have an increased risk of breast cancer," she said. "Their physicians may or may not know, but many physicians are not aware of the guidelines."

Moreover, many survivors don't know their radiation exposure, and she urged them to try to find those records from long, long ago.

The analysis - a report from the Childhood Cancer Survivor Study (CCSS) and the Women's Environmental Cancer and Radiation Epidemiology (WECARE) study - mined data on 1,268 women survivors of childhood cancers diagnosed from 1970 to 1986 and on 4,570 first-degree relatives of women who had survived at least 1 year after being diagnosed with breast cancer.

Median follow-up was 26 years in the childhood survivors, of whom 175 women were diagnosed with breast cancer as adults. Median latency was 23 years after treatment, and diagnosis was made at a median age of 38 years.

Multiple studies have shown an increased risk of breast cancer in women who received chest radiation as children, Dr. Moskowitz said. This large study has substantially longer follow-up and was surprising in the magnitude of risk it documents.

Chest radiation doses are lower today, and mantle field radiation - which had been used almost exclusively in Hodgkin's lymphoma - is no longer used, but other regimens are still in the clinic, she added.

Another surprise from the study was that whole lung radiation, even at low doses, can heighten breast cancer risk. "Women treated with whole lung radiation have a risk of breast cancer that is higher than previous recognized and may benefit from surveillance strategies," she said.

"These are striking data and certainly warrant our careful attention," commented press briefing chair Dr. Nicholas Vogelzang, chair and medical director of the developmental therapeutics committee at the Comprehensive Cancer Centers of Nevada, Las Vegas, and cochair of the genitourinary committee for U.S. Oncology Research.

"The benefit of curing a cancer is you can live 25 or more years," he said, noting that curves for breast cancer incidence rose after 25 years in a graphic representation of the data presented. "We have an obligation to those many thousands of young women whom we treated many years ago."

The investigators said that they had no relevant financial disclosures.

Platinum Levels Linked to Toxicity in Testicular Cancer Survivors

Major Finding: Circulating levels of platinum at 5 years were significantly higher in patients with elevated blood pressure (210 vs. 185 pg/g) and paresthesias (227 vs. 195 pg/g).

Data Source: Investigators did a longitudinal study of 96 consecutive patients treated with cisplatin for testicular cancer.

Presenting Author: Hink Boer, Department of Medical Oncology, University Medical Center Groningen, Groningen, Netherlands

Disclosures: Dr. Boer disclosed that he had no relevant conflicts of interest. Dr. Margolin disclosed that she is a consultant to Bristol-Myers Squibb, Genentech, and Johnson & Johnson.

BY SUSAN LONDON
IMNG Medical News

Long-term platinum exposure may explain higher rates of certain late adverse effects in men who have undergone treatment for testicular cancer, investigators report

based on a longitudinal study.

Among 96 consecutive men treated with cisplatin for testicular cancer, serum platinum levels 5 years later were 14% higher in those with elevated versus normal blood pressure and 16% higher in those with paresthesia versus those without it.

Dr. Hink Boer and his colleagues collected two or three serum samples and a 24-hour urine sample from the men at various time points after chemotherapy out to 13 years (median, 5 years) for platinum measurement.

The men had a median age of 29 years at the start of treatment, according to results reported in a poster presentation at the meeting. The median absolute cumulative cisplatin dose was 809 mg.

The findings are especially important as these survivors are young men who "have their whole life ahead of them, actually. Survivor care is very much focused on relapse detection, of course. In the last decade, I think there is more attention on the delayed effects," Dr. Boer, a research fellow in medical oncology at the University of Groningen in the Netherlands, said in an interview.

A population pharmacokinetic model using measured serum platinum concentration and urinary excretion rate, as well as administered cisplatin dosage, age, body surface area, height, and weight, suggested that the mean terminal half-life of platinum in serum was 3.7 years, Dr. Boer reported.

Platinum levels fell steadily and in exponential fashion with time after chemotherapy but were still detectable 13 years later. Serum platinum levels at 3 years and at 5 years after chemotherapy were significantly higher in men administered a higher total dose of cisplatin and in men having lower renal clearance, he said.

Analyses of long-term toxicity showed that, compared with their counterparts with lower blood pressure, men with a blood pressure of at least 130/85 mm Hg or on antihypertensive medication had higher mean serum platinum levels at 3 years (420 vs. 366 pg/g, P = .045) and at 5 years (210 vs. 185 pg/g, P = .04), as well as a higher platinum area under the curve (AUC) for years 1-5 (1,071 vs. 945 pg/g × 103 × day, P = .04).

Similarly, compared with their counterparts who did not have paresthesia, men having this adverse effect had higher mean serum platinum levels at 3 years (456 vs. 387 pg/g, P = .02) and at 5 years (227 vs. 195 pg/g, P = .02), as well as a higher platinum AUC for years 1-5 (1,144 vs. 996 pg/g × 103 × day, P = .02).

In contrast, men with secondary Raynaud disease and men with endothelial damage as assessed from von Willebrand factor levels did not have significantly higher serum platinum levels than their respective counterparts, Dr. Boer said.

"It is a well-known problem now that the chemotherapy has its late effects, and we wanted to look to see if these very small concentrations … have any relationship with these late toxicities," he said. "If you look at these data, you could assume that there is a relationship, a very small concentration but still, it might have an effect."

"The chemotherapy is very successful, of course; you don't want to change it. The cure rates are very high in testicular cancer patients," he added. "At the moment it is not possible to get the platinum out of the body. It is not technically possible to chelate it or something.

"But you have to think about it - it could be a mechanism, so it is worthwhile to do more studies on this. Perhaps in the future, it will be possible to chelate it and get it out, if we can confirm that this is really an etiological mechanism," he said.

Current practice at his institution for these patients is regular examinations with special focus on cardiovascular risk factors such as blood pressure and cholesterol. "We are trying to bring more structure in this care and to pay more attention to the late effects. I think [the patients] deserve it because they are so young," Dr. Boer said.

Discussant Dr. Kim Allyson Margolin of the University of Washington, Seattle, noted that accumulating research is casting doubt on the view that this chemotherapy has minimal late effects. However, despite the finding of an association between persistent free platinum and late toxicity, "we don't know whether the relationship of prior platinum exposure, just by doses given or something different about how the body handles the platinum related to renal function or metabolic polymorphisms, is responsible"

The study is "very interesting and provocative," Dr. Margolin concluded, "but we need more data. Pharmacologic investigations are still needed to enhance the quality of life for this growing number of germ cell tumor survivors."

Although the study focused on serum, Dr. Boer noted that platinum can be found in other tissues as well. "In the ganglia, for example, and also in bone, fat, and the liver … it's … not really known if the platinum in these body compartments is reactive or not. It is really a topic that deserves more research," he said.

Dr. Boer disclosed that he had no relevant conflicts of interest. Dr. Margolin disclosed that she is a consultant to Bristol-Myers Squibb, Genentech, and Johnson & Johnson.

When the Cancer Patient Isn't a Kid Anymore

Major Finding: Among adolescent and young adult cancer survivors, 97% said acceptance of their insurance was important or very important for making the transition to an adult physician's care.

Data Source: Investigators surveyed 103 survivors, aged 16-24 years, of pediatric cancers.

Presenting Authors: Karim Thomas Sadak, Children's National Medical Center, Washington, DC; Tara O. Henderson, University of Chicago Pritzker School of Medicine, Chicago, IL; Robert Michael Cooper, Kaiser Permenante, Los Angeles, CA

Disclosures: Dr. Sadak's study was funded by a Children's Health Center Board grant. Dr. Suh's study was funded by the NIH. The study by Dr. Cooper and colleagues was supported by Kaiser Permanente. All authors reported having no relevant conflicts of interest.

BY NEIL OSTERWEIL
IMNG Medical News

Every parent of a teenager has heard some variation of the demand, "Stop treating me like a kid!" The same can be said for adolescent and young adult survivors of childhood cancers, investigators say.

With childhood cancer survivorship rates hovering around 80% (according to Surveillance, Epidemiology and End Results data from 1996 to 2003), many patients are outgrowing their pediatricians and their pediatric oncologists. The patients still need regular follow-up, but just who will do that follow-up and how thoroughly is still an open question, said Dr. Karim Thomas Sadak, a pediatric oncology fellow at the Center for Cancer and Blood Disorders at Children's National Medical Center in Washington, D.C.

He and his colleagues surveyed 103 cancer survivors aged 16-24 years and asked them to identify what they found to be the most important factors in their decision to make the transition from a survivorship program at a children's hospital to a similar program at an adult institution.

"They told us some things we were very surprised to hear about their preferences for care. By far, the most commonly selected component of their clinical care that was rated as very important was the acceptability of their insurance. We might expect to hear that from 30-year-olds, but these people are most likely on their parents' insurance, as they are under 25," Dr. Sadak said in an interview at the annual meeting of the American Society of Clinical Oncology.

Based on the responses, Dr. Sadak and his associates asked a social worker who helps young patients make the transition to adult care to discuss insurance options with patients and their parents before and during patient visits and in follow-up.

"She gained knowledge about different insurances, reimbursements, copays, and policy issues related to survivorship care, and then she was able to proactively address these concerns with survivors" he said.

Survivors also rated flexible scheduling and comprehensive care as either very important or important. Paradoxically, while 97% of responders said that they wanted to make a transition that promoted independence, 96% wanted their primary childhood cancer provider present during the transition.

Conversely, "availability of vocational training and peer networking as well as considering readiness and a gradual introduction appear to be least important" factors in the decision to make the transition, Dr. Sadak said.

Internists Willing but Uncertain

In a different study, investigators from the United States and Canada surveyed U.S. internists about their knowledge of caring for childhood cancer survivors and found that most general internists said they are willing to follow adolescent and young adult survivors of childhood cancers but many also said that they would feel more comfortable doing so in collaboration with a cancer center.

Internists need to know that there are a wide variety of resources available to help them care for such patients, said coauthor Dr. Eugene Suh, a fellow in pediatric oncology at the University of Chicago Medical Center.

"Internists are really good at gathering information, but I don't think they necessarily know that this information is out there to help guide them in taking care of these cancer survivors," he said in an interview.

In their survey of a random sample of 2,000 U.S. general internists, 1,025 of whom responded, the investigators found that 72% of those who had seen pediatric cancer survivors in the past 5 years said they never received a treatment summary or survivorship care plan documenting diagnosis, cancer therapy, and plan for follow-up.

Additionally, on a 7-point scale rating familiarity with the Children's Oncology Group (COG) long-term follow-up guidelines, most respondents reported being "very unfamiliar" (mean score of 5.2 points) with the recommendations.

When presented with a clinical vignette of a female survivor of Hodgkin's lymphoma treated at age 16 with 25 Gy of mantle radiation and cumulative doses of doxorubicin 150 mg/m2 and cyclophosphamide 15 g/m2, 73% did not recommend yearly breast cancer surveillance, 85% did not recommend cardiac surveillance, and 23% did not recommend thyroid surveillance.

The investigators plan to conduct intervention studies aimed at improving general physicians' comfort with and knowledge of long-term care for survivors.

Research Resource

One source for survivorship studies could be vertically integrated health care systems, said Dr. Robert M. Cooper and colleagues from Kaiser Permanente Southern California in Los Angeles.

They found that, 5 years after diagnosis, 77% of 4,782 adolescent and young adult cancer patients were still being cared for by Kaiser physicians, as were 62% at 10 years.

"The lengthy insurance retention of adolescent/young adult cancer survivors makes a vertically integrated medical care system an ideal population laboratory for adolescent/young adult cancer survivorship research," they wrote in a poster presented at ASCO 2012.

Patient, Advocate for Thyself

Dr. Sadak said that patients also have to be willing to step up to the plate and act as their own best advocates.

"At some point, we as the provider want to educate the patient … to have some kind of responsibility for their own health care," he said. "The question is, at what age? It may not be 16, 17, or 18, especially in a population that's been through a serious illness like childhood cancer. The bonds that these patients and their parents have created are very strong. We have to respect that, while still encouraging the survivor to take responsibility for his health."

Dr. Sadak's study was funded by a Children's Health Center Board grant. Dr. Suh's study was funded by the National Institutes of Health. Dr. Cooper's study was supported by Kaiser Permanente. All authors reported having no relevant conflicts of interest.