

Oncology Week

In Review

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Rising Inappropriate Early Breast-Cancer Care Traced to Lumpectomy's Lapses

MILWAUKEE—Lumpectomy apparently stumbled out of the blocks on its way into widespread clinical use in this country.

The result, according to a study by a Medical College of Wisconsin team here, was a 10% drop in the proportion of women in the U.S. who received appropriate care for Stage I or II breast cancer between 1990 and 1995. As lumpectomy began to supplant mastectomy, appropriate care fell from 88% to 78%.

The problem, said internist Ann Butler Nattinger and colleagues, was that lumpectomy wasn't always performed in conformance with the standards of care set by a 1990 NIH consensus panel, a favorable review of lumpectomy that led to its increased popularity.

That panel said lumpectomy should be augmented by axillary node dissection and postop radiotherapy. Using SEER data on 144,759 women for whom appropriateness could be assessed, Dr. Nattinger's group found that skipping the ancillary treatment was the rub.

"Although the number of women treated each year for breast cancer in this [lumpectomy] cohort increased 13.6% from 1989 to 1995 (from 10,996 women in 1989 to 12,491 women in 1994), the number of women each year who received conservative treatment that did not satisfy the consensus guideline nearly doubled over the same period (from 1,158 women in 1989 to 2,207 women in 1995)," the Wisconsin team reported in the Sept. 30 *Lancet*.

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Triple-Drug Regimen Improves Survival in Metastatic Colon Cancer

NEW YORK—There's more published evidence that when irinotecan is added to first-line standard chemotherapy for metastatic colorectal cancer, it leads to a modest but significant improvement in survival.

The combination of irinotecan (Camptosar, Pharmacia), fluorouracil, and leukovorin resulted in longer progression-free and overall survival than 5-FU and leukovorin alone or irinotecan alone, according to a phase-3 trial of 667 patients published in the Sept. 28 *New England Journal of Medicine*. Preliminary results were presented at the 1999 ASCO meeting in Atlanta.

The multicenter North American study, led by Dr. Leonard B. Saltz of the Memorial Sloan-Kettering Cancer Center here, showed a 14.8-month median survival for the 225 patients randomized to the triple combo, vs. 12.6 months for 219 patients getting 5-FU and leukovorin, and 12.0 months for 223 patients getting irinotecan alone. The results were similar to those of a randomized trial in Europe of the three drugs vs. the standard first-line combo.

In the North American trial, getting the three drugs had a 39% probability of an objective response and had a median seven months without disease progression, vs. a 21% objective-response probability for the two-drug regimen alone

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In the Pipeline...

Prostate-cancer vaccine: a strong antibody response

Aphton of Woodland, Calif., said 90% of patients with locally advanced prostate cancer produced antibodies in a pilot study of its investigational vaccine, GnRH pharmacine. And 45% of the patients had a strong antibody response, the company reported at the CaP CURE Scientific Retreat in Incline Village, Nev., this week. Among the strongly responding patients, PSA levels dropped significantly and castration levels were achieved for up to nine months, the firm said.

Phase-3 trial for LymphoCide

Immunomedics of Morris Plains, N.J., said it is starting a phase-3 trial of LymphoCide (epratuzumab) for non-Hodgkin's lymphoma. LymphoCide, an anti-CD22 monoclonal antibody, will be tested in patients with low-grade or indolent disease who have failed or are refractory to other forms of therapy. The company expects another phase-3 trial of the agent for a more aggressive form of NHL to begin later this year. It also announced that the first patients have been enrolled in a phase-2 trial for the combination of epratuzumab and rituximab (Rituxan, IDEC, Genentech) in patients with indolent and aggressive NHL.

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Women Respond To Doctors' Advice On Colorectal Cancer Screening

SEATTLE—A little nudging by physicians could help to quadruple the rate of basic colorectal-cancer screening among women.

In a survey of 931 women between the ages of 50 and 80 at a Washington State managed-care organization, 64% of 527 who were encouraged by their physicians to be screened for colon cancer had a fecal occult blood test. In contrast, only 17% of 292 women whose physicians never mentioned screening had an FOBT.

Twenty-four percent of the women who had never been screened said it was because their doctor had never recommended the test, said Dr. Margaret Mandelson of the Center for Health Studies Group Health Cooperative here and colleagues. Eighty-four percent of these women said that they would be more likely to have an FOBT if their physician suggested it, they reported in the Oct. 1 *American Journal of Preventive Medicine*.

The researchers found that screening participation did not vary by perceived or actual risk of the disease. But those with a family history or who were knowledgeable about the risk factors of colorectal cancer were more likely to be screened, and not just by FOBT.

Among the women surveyed, 25% had never had an FOBT, and 48% had been screened in the two years prior to interview. Fifty-eight percent of the women said that their primary-care physician had encouraged them to be screened.

A Case Against Specimen Radiography in Breast Cancer

DUARTE, Calif.—A team of academic surgeons here has questioned the benefit of specimen radiography during needle/dye-localized biopsies for breast cancer.

A retrospective analysis of the needle/dye-localized needle biopsies found that only three of 165 patients (1.8%) benefited from specimen radiography performed during the procedure, say Dr. Lawrence D. Wagman and colleagues of the City of Hope National Medical Center.

For two patients, specimen radiography prevented an additional surgical procedure and in one patient diagnosis could have been delayed had the procedure not been done, the team reported in the September *Archives of Surgery*.

The City of Hope team argues that specimen radiography adds time to the operation, an average of 20 minutes and a range up to 59 minutes in the study, plus significant cost. They say that in 83.6% of the patients the entire lesion was removed by the first excision, and even when specimen radiography identified problems additional excision was limited.

In 17 patients specimen radiography identified a partial lesion or a close margin, prompting further excision in three patients. In another 10, specimens contained no lesion leading to further excision in six patients. No malignancies were missed in the study. "To continue the current standard is expensive, time-inefficient, and plagued with an unacceptable number of incorrect studies," they concluded.

But others disagreed. In an invited commentary, surgeon Ronald Latimer of the Sansum-Santa Barbara (Calif.) Medical Foundation Clinic questioned the researchers' definition of beneficial, noting that he sees the purpose of the procedure as confirming the removal of suspicious lesions. Using this criterion, the procedure was beneficial, he said.

Radiologist Barbara Monsees of Washington University in St. Louis had similar concerns.

She feels that abandoning specimen radiography would result in the delay in diagnosis of breast cancer for some women whose lesions are not removed at surgery, and it would expose surgeons to legal liability.

Not all needle/dye-localized breast biopsies are performed by experts, Dr. Monsees says, and the City of Hope team overlooked the role of specimen radiography at community-based cancer centers. In addition to documenting removal, specimen radiography can also help the surgeon and pathologist in other ways, she adds.

Dr. Wagman rejoins that the purpose of the study was to evaluate whether specimen radiography changes intra-operative decisions. He acknowledges that surgeons use specimen radiography to confirm that they have done a good job and have removed the entire mass. But he says that this "feel-good factor" isn't enough justification for a procedure that usually doesn't lead to further steps.

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A phase-3 for OraTest

Zila of Phoenix announced that the phase-3 study protocol for OraTest, an oral-cancer detection product, was approved, and patient enrollment will begin shortly. The company is expecting to enroll 600 patients in this international study to compare OraTest to visual exam alone. OraTest uses Zila Tolonium Chloride to selectively stain squamous-cell carcinoma.

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Liposuction for Lymphedema?

BRUSSELS—Breast-cancer patients with lymphedema may benefit from liposuction of arm tissue.

A six-year follow-up of 64 women treated with a novel Swedish lymphedema therapy that uses liposuction showed that the average affected arm wound up 4% smaller than the contralateral arm, Dr. Haken Brorson and colleagues of Malmo University Hospital said this week.

The procedure involves 20 small incisions about 2 cm long to remove fatty tissue and accumulated lymph, an average of 1.8 liters, Dr. Brorson told the European Breast Cancer Conference here. The women had the procedure after suffering from grade 2 or 3 lymphedema for an average of nine years.

Two weeks after surgery, arm swelling was reduced by an average of 72%, and after a month it was 80%, Dr. Brorson reported. The average reduction was 88% after three months, 93% after six months, and 98% after a year. Lymphedema recurred in none, but patients must wear a custom-made compression sleeve permanently to maintain the size reduction.

Patients reported increased range of motion, decreased pain and discomfort, improvement in skin-blood flow, and improved daily life. There was no change in lymph transport capacity, Dr. Brorson added.

Radiotherapy for Women With BRCA Mutations: No Problems

ANN ARBOR, Mich.—Women with BRCA 1 and 2 mutations can apparently have lumpectomy plus radiotherapy for early breast cancer without concern that the radiation will complicate treatment or trigger a recurrence.

Looking to see whether women with BRCA mutations exposed to ionizing radiation had a greater susceptibility to radiation-related complications or breast-cancer recurrence (a theoretical possibility), a retrospective cohort study found they didn't, a nine-center North American team said this week.

The study of 54 women with a BRCA1 mutation and 17 with a BRCA2 mutation, all with Stage I or 2 breast cancer, showed five-year actuarial local-control, relapse-free survival, and overall-survival rates after lumpectomy and radiotherapy that were comparable with those of 213 matched controls who didn't have BRCA mutations. Radiation-associated complications were also comparable.

Indeed, there was a 2% local-failure rate after five years in the genetic cohort, vs. a 4% rate among the controls, radiation oncologist Lori J. Pierce of the University of Michigan and colleagues reported in the Oct. 1 *Journal of Clinical Oncology*. Preliminary results were reported at the 1999 ASCO meeting in Atlanta.

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This was a jump from about 10% of the cohort in 1989 to 19% in 1995. Dr. Nattinger said the results suggest that more than 22,000 women a year may be receiving less-than-optimal initial treatment for early breast cancer, most of it because of inappropriate lumpectomy care.

Roughly equal proportions of women who had a lumpectomy didn't receive radiotherapy or axillary-node dissection, or both, Dr. Nattinger said. The decline in appropriate treatment was seen in all subgroups—age, race, disease stage, and population density.

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Foscan is denied

Scotia Holdings has been denied FDA approval of Foscan (temoporfin, mTHPC) for head-and-neck cancer. The FDA declined to elaborate on its decision until it meets with the company. The news hit the financially strapped company hard, causing its stock to plummet more than 60%. Foscan, a photosensitizing agent that is activated by light from a laser, is awaiting European approval.

Trisenox gets nod

Cell Therapeutics of Seattle received FDA approval of Trisenox (arsenic trioxide) for acute promyelocytic leukemia. In clinical trials, 28 of 40 patients with this rare leukemia went into remission after receiving Trisenox. Forty percent of the patients had an increased QT interval while taking the drug, prompting the FDA to suggest that patients be closely monitored. The company expects that Trisenox will be available in the next three weeks.

So does Zometa

Novartis of East Hanover, N.J., has received an approvable letter from the FDA for Zometa (zoledronic) for hypercalcemia of malignancy. The FDA has requested additional information, including serum creatinine data from an ongoing trial for the treatment of bone metastases. Zometa, an IV bisphosphonate, is an enhancement of Novartis' HCM drug Aredia (pamidronate). In trials, 88.4% of patients taking Zometa responded, compared with 70% of patients given pamidronate, according to the company. The drug was recently approved in Canada.

Good start for Leuvectin

Vical of San Diego said PSA levels of two of the first six prostate-cancer patients in a phase-2 trial of Leuvectin slowed or stopped rising. Leuvectin is a gene-based immunotherapy for patients who do not respond to radiation, and the early phase-2 data were presented at the CaP CURE Scientific Retreat in Incline Village, Nev., this week. Patients are being enrolled in the trial at UCLA and the Cleveland Clinic.

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Aptosyn is denied

Cell Pathways of Horsham, Pa., received a “non-approvable” letter from the FDA for Aptosyn (exisulind) for familial adenomatous polyposis (FAP). Cell Pathways said that the FDA found problems in the “clinical portion” of the NDA, and that it will discuss the letter in the next two weeks with the FDA. Aptosyn is a selective apoptotic anti-neoplastic drug that Cell Pathways says it is testing for several cancer and precancer indications.

Melanoma vaccine rolled out

Genzyme Molecular Oncology of Framingham, Mass., is starting a phase-1/2 trial of a gene-therapy melanoma vaccine. An adenovirus vector will deliver MelanA/MART1 and gp100 antigens. The company is recruiting patients in Boston and Dallas and expects to enroll 36 patients with Stage II, III, or IV disease.

Marimastat: more bad news

British Biotech of Oxford released phase-3 results of marimastat for advanced ovarian cancer. When the oral matrix metalloproteinase inhibitor was given in combination with carboplatin, patients showed no significant advantage over those given carboplatin alone. Previously, phase-3 trials of the agent for glioblastoma showed no advantage.

More paclitaxel

Bigmar of Johnstown, Ohio, has filed an ANDA with the FDA for generic paclitaxel. According to the company, its barrier isolation technology increases the sterility of generic drugs, leading to a higher-quality product and lower manufacturing costs. Bigmar is the second company to file for FDA approval of generic paclitaxel following the approval of Ivax’s version of the drug.

Leuprolide’s phase-3 moves on

Atrix Laboratories of Fort Collins, Colo., presented interim data on 51 of 120 patients in a phase-3 study of Leuporgel (leuprolide) for prostate cancer, showing that the LHRH agonist has dropped testosterone levels below 20 ng/dL after six injections at 30-day intervals. The data were given at the CaP CURE Scientific Retreat in Incline Village, Nev., this week. Leuporgel is an injectable liquid that solidifies inside the body, releasing the agent continuously as it is absorbed.

Rituxan’s label revisions

IDEC Pharmaceuticals of San Diego and **Genentech** of South San Francisco have received a “completed review” letter from the FDA for Rituxan (rituximab). This letter was in response to a supplemental BLA submitted in late 1999 seeking approval of the agent for the treatment of bulky non-Hodgkin’s lymphoma, a weekly dosing regimen, and multiple courses of treatment for NHL. Rituxan has been FDA-approved since 1997 for relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL.

A phase-2 for iroflufen

MGI Pharma of Minneapolis has begun a phase-2 trial of iroflufen (MGI 114, hydroxymethylacylfulvene), a chemotherapy agent for liver cancer. The trial at Beth Israel Deaconess in Boston is still enrolling patients with inoperable liver cancer. In phase-1 trials, stable disease for some patients was maintained for nearly five months, and in other phase-2 trials there was tumor shrinkage for some patients with liver metastases. The company says that iroflufen shows early signs of activity in chemoresistant tumors.

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and four months without disease progression. For those who were given irinotecan alone, it was 18% and four months.

The three drugs were given weekly for four weeks every six weeks. For those getting the two drugs alone, administration was five days a week every four weeks. Irinotecan alone was given weekly for four weeks every six weeks. Some 22.7% of the three-drug patients had grade 3 or 4 diarrhea, compared with 13.2% of those given two drugs. The difference was primarily in grade 3. Grade 4 neutropenia among the triple-drug group (24.0%) was about half of that for those getting two drugs (42.5%).

In an accompanying editorial, Dr. Robert J. Mayer of the Dana-Farber Cancer Institute in Boston said the study “demonstrates that progress, albeit slight, has at last occurred” for advanced colorectal cancer. He said the three-drug combo “might possibly represent a new standard of care.” But if the goal of therapy is palliation, he suggested that perhaps the improvement could be achieved with less toxicity by giving the drugs sequentially instead of concomitantly.

O-Vax is an orphan

Avax of Kansas City has received orphan-drug status for O-Vax, an individualized vaccine for ovarian cancer. The vaccine is in phase-2 trials as an adjuvant therapy. In initial trials, eight of 10 patients with advanced disease had an immunological response.