This is part of an occasional series that recalls some of the stories reported 10 years ago in the News section of the Journal.

This September, results of a phase III study of the shark cartilage extract AE-941 (Neovastat) suggested no benefit of the product on overall survival of patients with renal cell cancer. The findings come as a disappointment to researchers in a field plagued by negative publicity.

Shark cartilage gained widespread attention in 1993 when the television news program “60 Minutes” broadcast a story on shark cartilage as a promising treatment for cancer. The centerpiece was a Cuban study that reported that 3 of 29 patients with cancer responded to shark cartilage treatments. In the Aug. 4, 1993 issue of the Journal, the News spoke with experts who dismissed the findings as unreliable and criticized “60 Minutes” for sensationalizing the treatment.

In fact, subsequent studies have found no benefit of shark cartilage for the treatment of cancer. In a 1998 study in the Journal of Clinical Oncology, researchers reported that shark cartilage was no more effective than supportive care in 60 patients with various advanced cancers, including breast, colorectal, lung, prostate, and non-Hodgkin’s lymphoma. Moreover, the treatment had no noticeable effects on quality of life. And in 2000, Danish researchers reported at the European Breast Cancer Conference that shark cartilage was ineffective in women with advanced breast cancer.

Still, there was a concern that shark cartilage products were being used outside of the clinical trial setting by patients with cancer. In 2000, the National Cancer Institute launched a randomized phase III trial to test the effects of AE-941—a pharmaceutical agent that has demonstrated antiangiogenic activity in preclinical studies—in combination with chemotherapy and radiotherapy in 756 patients with unresectable non–small-cell lung cancer.

“This is the first time in which a shark cartilage product has been looked at in a randomized controlled trial for cancer,” said Jeffrey White, M.D., director of the Office of Cancer Complementary and Alternative Medicine at the National Cancer Institute. He added that he hopes the findings will provide a clearer assessment of shark cartilage’s clinical value.

Charles Lu, M.D., a lung cancer specialist at the University of Texas M. D. Anderson Cancer Center in Houston and principal investigator of the trial, said that some researchers are skeptical of AE-941 because it is a standardized extract rather than a purified molecule. He said that accrual to the trial has been slow and part of the challenge has been overcoming physicians’ negative perception of shark cartilage–based products.

The latest results on AE-941 in renal cell cancer have added to the pessimism. But Lu pointed out that renal cell cancer and lung cancer are very different diseases, and he noted that in the renal cell cancer trial there appeared to be some benefit in a subgroup of patients with limited metastatic disease. He said that he is optimistic and that he hopes to have results of the lung cancer trial in 5 years: “Whether it’s negative or positive data, hopefully we’ll at least learn something valuable about how much further to pursue cartilage-based products.”

Controversial Treatment

Like shark cartilage, high-dose chemotherapy is a field fraught by negative publicity.

In the July 7, 1993 issue of the Journal, the News reported that an
international panel had concluded that high-dose chemotherapy with bone marrow transplantation should not be considered standard therapy for any of the nine cancers they examined. These included non-Hodgkin’s lymphoma; Hodgkin’s disease; acute myeloid leukemia; acute lymphocytic leukemia; breast, ovarian, and testicular cancers; glioma; and small-cell lung cancer.

Since then, researchers have determined that high-dose chemotherapy may be used as standard treatment for relapsed large cell lymphoma and relapsed Hodgkin’s disease. And a study in the May 8, 2003 issue of the New England Journal of Medicine suggested that high-dose chemotherapy and stem cell transplantation is more effective than standard therapy in patients with multiple myeloma.

Where the value of high-dose chemotherapy remains controversial is in solid tumors, and nowhere is this controversy more visible than in advanced breast cancer.

“I think that unfortunately this was an area that was put out in the public eye with little information and with very little follow-up, and I think it poisoned interest among oncologists,” said Scott Bearman, M.D., Ph.D., director of the Bone Marrow Transplant Program at the University of Colorado in Denver.

In 1999, four randomized studies presented at the American Society of Clinical Oncology annual meeting reported no survival advantage of high-dose chemotherapy in patients with advanced breast cancer. And in July 2003, two studies in the New England Journal of Medicine suggested that high-dose chemotherapy and stem-cell transplantation had no effect on overall survival in women with high-risk breast cancer.

But what some studies also found is that there may be a subset of women under the age of 50 in which high-dose chemotherapy may delay relapse and improve relapse-free survival. Naoto T. Ueno, M.D., Ph.D., director of bone marrow transplantation in breast cancer at M. D. Anderson Cancer Center, said that this data should not be ignored. He said that there is enough data to warrant continued investigation in this field if trials are better designed.

William P. Peters, M.D., Ph.D., president emeritus of the Barbara Ann Karmanos Cancer Institute in Detroit, Mich., recommended that future studies look specifically at women under the age of 50 and that these studies should have adequate follow-up time.

Bearman agreed that more research should be done, but acknowledged that it may be difficult to find support for such studies. “While it may seem like a good idea to do another study, there may be resistance to doing it. Not a lot of people want to do a study where the outcome may only differ after 10 years or longer,” he said.

Patient advocacy groups are taking a cautious approach: “The responsible thing for us to do right now is to encourage women to be informed, talk with their doctors about [high-dose chemotherapy], and should they chose to go this way in their treatment plan, to be sure that they understand the risks and potential benefit and that they hopefully will do it in a well-designed clinical trial atmosphere,” said Cheryl Perkins, M.D., senior clinical adviser at the Susan B. Komen Breast Cancer Foundation.

**Following Farmers**

In the Feb. 3, 1993 issue of the Journal, the News announced the initiation of the Agricultural Health Study (AHS), a 10-year, $15 million study funded by NCI, the National Institute of Environmental Health Sciences, and the U.S. Environmental Protection Agency to examine the role of agricultural exposures in the development of cancer and other diseases in the farming community.

Ten years later, major findings from AHS are just beginning to be published, and the first publication on pesticides and cancer suggests that there may indeed be an association.

In the May 1 issue of the American Journal of Epidemiology, NCI’s Michael Alavanja, Dr.P.H., and his colleagues reported that pesticide applicators (e.g., farmers, nursery workers, and people employed by pest control companies) had a 14% increased risk of prostate cancer compared with the general population in Iowa and North Carolina, the states involved in the study.

Although only one chemical, methyl bromide, was associated with prostate cancer risk in all groups studied, a number of other pesticides were associated with an increased risk of prostate cancer among men with a family history of the disease.

“People are looking to this study to finally give a really clear picture as to what chemicals are associated with cancer and to vindicate others that are not,” said Alavanja. He added that a major paper on lung cancer will be published next year.

Because of the study’s large size—nearly 90,000 agricultural workers and their wives—it can answer questions with unprecedented power, he said. He added that the next 5 years will yield an incredible amount of information, including the identification of new carcinogens. “We’re just at the point where we’re going to be making major statements,” said Alavanja.

He said that they are also trying to identify the mechanisms by which certain chemicals cause cancer. The information can be used to help manufacturers produce safer chemicals.

Meanwhile, other researchers are working to disseminate the new findings to the farming community.

“The message all along has been that it’s prudent to reduce your exposure and also to reduce the exposure of those around you,” said Amy Brown, Ph.D., immediate past president of the American Association of Pesticide Safety Educators and a professor at the University of Maryland, College Park.

“Now we have documentation that it actually makes a difference.”

—Linda Wang