Celecoxib May Prevent Skin Cancer, Study Finds

BY KATE JOHNSON

MONTREAL — A twice-daily dose of celecoxib given over a period of 9 months was associated with a 60% reduction in the incidence of nonmelanoma skin cancer, according to the results of a new study.

"Inhibition of COX-2 [cyclo-oxygenase-2] is an effective means of limiting the development of cutaneous squamous and basal cell carcinomas in humans," reported Dr. Craig Elmets at the annual meeting of the Society for Investigative Dermatology.

The findings suggest that pharmaceutical agents such as celecoxib may offer greater protection against skin cancer than sunscreens, which are only "modestly effective," said Dr. Elmets, professor and chair of the department of dermatology and director of the Skin Disease Research Center at the University of Alabama, Birmingham.

"There's only about a 35% reduction in squamous cell carcinomas when sunscreens are used on a regular basis over a 5-year period of time, and there's no reduction in basal cell carcinomas."

The multicenter, randomized, placebo-controlled study was funded by the National Cancer Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, with additional funding from Pfizer through a contractual agreement with the National Institutes of Health, he said. Dr. Elmets did not disclose any personal conflicts of interest.

The study enrolled 238 patients with nonmelanoma skin cancers from eight U.S. centers. The mean age of the patients was 65 years, most were male, and virtually all were white.

"The study was terminated somewhat early because of concerns of cardiovascular effects due to another COX-2 inhibitor," he noted.

Subjects in the study had Fitzpatrick skin types I-III, extensive actinic damage with 10-40 actinic keratoses (AK), and a prior histologic diagnosis of either AK or nonmelanoma skin cancer. Subjects were excluded if they required treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), although cardioprotective doses of aspirin were allowed.

At entry, patients had a mean number of 22 AKs, as well as between 2.1 and 2.5 nonmelanoma skin cancers, he said.

Celecoxib had no effect on the number of actinic keratoses, but there was a 58% reduction in basal and squamous cell carcinoma incidence, compared with placebo-treated controls.

Patients were randomized to either placebo or celecoxib 200 mg twice daily, which is the approved dosage for arthritis, said Dr. Elmets. "We were concerned about cardiovascular abnormalities and GI abnormalities, and if anything there was a bias towards patients in the celecoxib group having a prior history of that."

A comparison of the number of AKs at baseline and completion showed a lack of effect of celecoxib, compared to placebo, he noted. However, the development of new cutaneous basal and squamous cell carcinomas was much reduced. "We were delighted to find that celecoxib was quite effective, with a 58% reduction, compared to placebo-treated controls," he said.

Looking at the two types of lesions separately, treatment with celecoxib resulted in a 58% reduction in squamous cell carcinomas (SCC), and a 62% reduction in basal cell carcinomas (BCC).

"The difference between the [placebo and treated] groups started to become apparent quite rapidly, at 3 months, and persisted throughout the study.

"We were concerned that there might be one or two outliers that were skewing the results, so rather than looking at the total number of skin cancers, we also looked at the number of individuals who developed BCC or SCC or both. Again we found that patients with celecoxib had fewer BCCs and SCCs than" placebo patients.

There were no differences in adverse events including cardiovascular adverse events between the two groups, Dr. Elmets reported. During the question period, he acknowledged that there were higher blood pressures reported in the treatment group.

Of the 238 patients enrolled, 36 withdrew from the treatment group and 24 withdrew from the placebo group. The major reasons for withdrawal were disease progression, withdrawal of consent, the use of an excluded medication, an adverse event, and loss to follow up.

"The data is very compelling," said Dr. Maryam Asgari of Kaiser Permanente in Oakland, Calif., in an interview. But she suggested perhaps the study was too short to have such dramatic conclusions. "I know that typically for most cancers you would need a study to last 2-5 years before you would expect to measure an effect," she said. Similarly, adverse events from COX-2 inhibitors would likely need longer to develop.

Dr. Asgari said her research in the same field has produced the opposite results.

A study that she has just completed found no protective effect for all NSAIDs—both selective and nonselective COX inhibitors—on the incidence of squamous cell carcinoma. And a previous paper published by her group also found no protective effect of these drugs on melanomas (J. Natl. Cancer Inst. 2008;100[13]:967-71).

In addition, she said celecoxib's lack of effect on AKs is a puzzling result. "You would think that if COX-2 inhibitors are working to prevent new cancers from arising that they would also have a pretty dramatic effect on actinic keratoses because they both share the same pathway." ■

Sentinel Lymph Node Biopsy Proves Beneficial for Some

BY ALICIA AULT

AUSTIN, TEX. — Conducting sentinel lymph node biopsies in melanoma can provide significant benefits, but it is not advisable for the majority of patients, said Dr. Christopher Bichakjian.

The wisdom of conducting an SLNB in melanoma has been extensively debated, Dr. Bichakjian said at the annual meeting of the American College of Mohs Surgery.

Some suggest that melanoma metastasis to regional lymph nodes and visceral organs occur in a parallel fashion, he said. According to this hypothesis, occult disease in a lymph node is merely a marker of distant metastatic disease.

But most believe melanoma metastasis occurs in a more orderly fashion. Following this hypothesis, microscopic disease in the sentinel node represents the earliest stage of metastasis; early treatment in this instance may provide a survival benefit.

Dr. Bichakjian, director of the Multidisciplinary Merkel Cell Carcinoma Program at the University of Michigan in Ann Arbor, acknowledged that both scenarios could occur.

The "majority of patients with melanoma are not, and will never be, a candidate for this procedure," he said.

Most patients are diagnosed at an early stage in which the low risk of metastasis would not justify an SLNB, he said. Moreover, searching for occult metastatic disease in an elderly patient with multiple comorbidities would not outweigh the risk of surgery under general anesthesia, said Dr. Bichakjian.

But there are good reasons for considering SLNB in selected patients with melanoma. It is a "powerful—if not the most powerful—independent factor predicting survival," he said.

Dr. Bichakjian cited a study in patients with Merkel cell carcinoma. Those who were pathologically node negative had a 5-year survival of 97%, compared with 52% for patients with pathologically confirmed nodal metastases (J. Clin. Oncol. 2005;23:2300-9).

He also said that many people have undervalued the significance of the Multicenter Selective Lymphadenectomy Trial (MSLT-I) by simply stating that there was no difference in overall survival, and ignoring the fact that it was an interim analysis (N. Engl. J. Med. 2006;355:1307-17). The disease-free survival, however, was significantly greater in patients who had an SLNB.

Among those with nodal metastases, patients with a positive SLNB and early lymph node dissection had a significantly better survival than patients in whom dissection was performed at the time of clinically apparent disease, even when corrected for a false-negative rate.

A lead time bias may explain the difference in nodal metastasis rate between the SLNB and observation arms in the interim analysis, he said.

For melanomas greater than 4 mm in Breslow thickness, there is a prognostic benefit of SNLB, contrary to popular wisdom, said Dr. Bichakjian. There is still no model accurate enough to predict which patients with a positive SLNB will have additional positive nodes, he said.

Until MSLT-II provides more data, all patients with a positive SLNB should undergo complete lymphadenectomy. Additional positive non-sentinel nodes may provide further prognostic information, he said.

The sentinel lymph node may be key if, as has been suggested, that lymph node is immunologically suppressed under the influence of cytokines produced by the primary tumor, he said. If this downregulation precedes the establishment of nodal metastases, it may in fact be a prerequisite for metastasis. If this is true, early therapy to prevent immune suppression in the regional nodal basin might prevent the spread of melanoma.

At the University of Michigan Multidisciplinary Melanoma clinic, the criteria for SLNB include clinically-localized melanoma greater than 1 mm in Breslow thickness in a patient without significant morbidities and no previous wide excision. SLNB is considered in patients with melanomas between 0.75-0.99 mm only in the presence of other adverse parameters, particularly young age, high mitotic rate, and angiolymphatic invasion.

SNLBs have been performed at the clinic for a wide range of patients including those with head and neck melanoma, vulvar melanoma, conjunctival melanoma, and pediatric patients, among others, Dr. Bichakjian said.

Given that only a small percentage of patients with melanoma will be a candidate for SLNB and that a smaller number will have positive SLNB results, one might question the worth of doing the procedure, but he noted that when breast cancer patients were surveyed as to what would make it worth going through 6 months of adjuvant chemotherapy, 50% said just a 1-day improvement in survival.

There often is a disconnect between what the patient and provider prefers. Providers should be cognizant of that difference, before dismissing the prognostic value and potential survival benefit of SLNB, said Dr. Bichakjian, who reported no conflicts. ■