Sorafenib Results Mixed For Advanced Melanoma

BY BRUCE K. DIXON
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CHICAGO — The first two randomized trials to assess the addition of sorafenib to chemotherapy for advanced melanoma exhibited mixed results, according to presentations at the annual meeting of the American Society of Clinical Oncology.

A randomized, 17-center, phase II study of 101 chemotherapy-naive patients showed a 50% improvement in progression-free survival and a 62% improvement in time to progression when sorafenib (Nexavar) was added to dacarbazine (DTIC-Dome) compared with dacarbazine plus placebo.

A 6-month progression-free survival rate of 41% 'is truly the high water mark of what we've achieved to date ... at least when focusing on this end point.'

Improved progression-free survival did not translate into a survival benefit, however. "At our last analysis, 65 of 101 patients had died, and there was no difference in median survival between the two study arms," said Dr. David F. McDermott, clinical director of the biologic therapy program at Beth Israel Deaconess Medical Center in Boston.

The second study, the 270-patient, phase III Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial, tested paclitaxel plus carboplatin with or without sorafenib as second-line treatment. The trial produced negative results. Dr. Sanjiv S. Agarwala, chief of medical oncology at St. Luke's Cancer Center in Bethlehem, Pa., reported that sorafenib failed to improve progression-free survival, tumor response rates, or time-to-disease progression in metastatic melanoma patients, whose disease had progressed on a chemotherapy regimen containing dacarbazine or temozolomide (Temodal).

In his discussion of the two trials, Dr. Keith Flaherty said that although the trials had mixed results, the 6-month progression-free survival rate of 41% in the study by Dr. McDermott and colleagues "is truly the high water mark of what we've achieved to date ... at least when focusing on this end point." These gains were achieved at a toxicity cost deemed "not unacceptable" by Dr. Flaherty of the division of hematology-oncology at the University of Pennsylvania Health System in Philadelphia.

The multicenter trial by Dr. Agarwala and colleagues did manage to produce data showing that the carboplatin-paclitaxel combination is "relatively active" in patients who have failed front-line chemotherapy containing dacarbazine or temozolomide, according to Dr. Flaherty. "The roughly 30% progression-free survival rate at 6 months is a number that many of us in the field believe is a sign of activity," he said.

"The front-line randomized phase II trial certainly suggests that sorafenib may be active in this setting, and I think the phase III study gives us enough evidence to say that carboplatin-paclitaxel control arm therapy is a perfectly reasonable therapy to offer patients," Dr. Flaherty concluded.

In the dacarbazine with or without sorafenib study, Dr. McDermott and his associates randomized 101 good performance status patients to receive either dacarbazine at 1,000 mg/m^2 on day 1 in combination with oral sorafenib 400 mg twice daily, or dacarbazine at 1,000 mg/m^2 on day 1 and two placebo tablets twice daily. Tumors were assessed at baseline and every 6 weeks, and treatment was continued until progression or intolerable toxicity.

Dose reductions due to adverse events (including grades 3 and 4 thrombocytopenia, neutropenia, nausea, and CNS hemorrhage) were more common in the sorafenib arm.

"All these toxicities were reversible, and there were no treatment-related deaths. Sorafenib-associated hand-foot syndrome, rash, hypertension, and elevated lipase [were] not greater than [have] been reported in earlier sorafenib trials," Dr. McDermott said.

The 270 chemotherapy-refractory patients in the PRISM trial had stage IV or unresectable stage III melanoma. Half were randomized to receive paclitaxel 225 mg/m^2 and carboplatin AUC = 6 on day 1 every 3 weeks plus oral sorafenib 400 mg twice daily on days 2 to 19 every 3 weeks. The other half received the paclitaxel-carboplatin regimen plus an oral placebo. Both groups continued treatment until disease progression or intolerable toxicity.

The difference in progression-free survival between the sorafenib plus chemotherapy and sorafenib plus placebo arms was insignificant at 17.4 weeks and 17.9 weeks, respectively, and there were no tumor responses in either arm, according to Dr. Agarwala.

Neutropenia affected nearly half of patients similarly in both arms, while thrombocytopenia, diarrhea, hand-foot reactions, and rash were higher with sorafenib.

Both trials were sponsored by Bayer, which markets sorafenib. The ongoing Eastern Oncology Cooperative Group trial E2603 is evaluating the same regimen studied by Dr. Agarwala and colleagues in a larger patient population with unresectable locally advanced or stage IV melanoma. ■

Plant-Based Compound Shows Efficacy Against Basal Cell Ca

BY JOHN R. BELL
Associate Editor

NEW YORK — A recently discovered chemical in the sap of a weed common to North America and much of the world appeared safe and effective in treating patients with superficial and nodular basal cell carcinoma, according to results presented as a poster at the American Academy of Dermatology's Academy 2007 meeting.

Using the PEP-005 extract of the petty spurge plant (*Euphorbia peplus*), Dr. Robert H. Rosen, a dermatologist in private practice in Sydney, Australia, and his colleagues, with sponsorship from Peplin Ltd., the manufacturer of the extract, conducted two separate multicenter, randomized, controlled, double-blinded, parallel phase-IIa trials for treatment of superficial basal cell carcinoma (sBCC) and nodular basal cell carcinoma (nBCC).

They recruited 58 patients with nBCC and 60 with sBCC. All participants were white adult women with one basal cell carcinoma on the arm, shoulder, chest, face, neck, abdomen, back, leg, or scalp.

The sap of petty spurge (*Euphorbia peplus*) has been used in traditional medicine as a cure for warts.

Patients were given a gel vehicle containing one of three concentrations of the drug: 0.0025%, 0.01%, and 0.05%. Each patient received two doses, either on 2 consecutive days or with the second dose 1 week after the first.

Application of the 0.05% concentration PEP005 topical gel overall showed the greatest efficacy in both types of BCC after 85 days, regardless of dosing schedule, Dr. Rosen and colleagues reported.

In the nBCC group, the two dosing schedules combined achieved complete histologic clearance of 25% of lesions (in 4 of 16 patients) and complete or marked clinical clearance (defined as 50%-90% improvement) in 38% of lesions (6 of 16 patients). For sBCC, the two regimens of 0.05% PEP005 achieved complete histologic clearance in 50% (8 of 16 patients) and complete or marked clinical clearance in 69% (11 of 16 patients).

There were no significant differences in safety between the dosing schedules. Among patients with nBCC, the most common local skin response was erythema, with 50% of the 0.05%-strength patients reporting moderate levels and 19% reporting severe erythema. Other responses reported for the 0.05% concentration were itch (moderate in 31% and severe in 0%), edema (31% moderate and 0% severe), scabbing/crusting (31% and 0%), and flaking/scaling/dryness (38% and 6%).

In the patients with sBCC, local skin reactions for the 0.05% PEP005 gel were itch (19% moderate and 0% severe), erythema (63% and 0%), edema (13% and 0%), scabbing/crusting (50% and 6%), flaking/scaling/dryness (25% and 13%), and moderate hypopigmentation (an adverse effect not reported in the nBCC group) in 13%. ■

U.K. Study Data Confirmed Safety of Diclofenac 3% for Actinic Keratosis

AMSTERDAM — Diclofenac 3% gel was well tolerated and showed an excellent safety profile for treatment of multiple actinic keratoses in a postmarketing safety surveillance study.

The study, conducted in 140 primary care practices in the United Kingdom, showed no severe treatment-related adverse events in 450 treated patients. The most common adverse events were mild to moderate dry skin, itching, and redness, each occurring in 16%-20% of patients, Dr. Ron Higson reported at the 11th World Congress on Cancers of the Skin.

Severe versions of these side effects occurred in fewer than 4% of patients, added Dr. Higson of Clitheroe (U.K.) Health Centre.

Participants in this observational study were instructed to apply diclofenac 3% gel (Solaraze) twice daily for 12 weeks to areas of actinic keratoses (AKs). The topical nonsteroidal anti-inflammatory drug is licensed for treatment of AKs in the United States, United Kingdom, and some other European countries. Patients were assessed during office visits at baseline and at weeks 6, 12, and 16.

Although this was designed primarily as a safety study, there was a secondary efficacy end point consisting of change over time in the longest AK axis from each patient's three largest AKs. The mean reduction in the size of AKs located on the head, face, or neck was 2.8 mm at week 6 and 6.4 mm at the week 16 follow-up visit, Dr. Higson said at the congress, which was cosponsored by the Skin Cancer Foundation and Erasmus University, Rotterdam, the Netherlands.

The study was funded by Shire Pharmaceuticals.

Dr. Eggert Stockfleth, director of the skin cancer center at Charité University Hospital, Berlin, commented that diclofenac gel's two major advantages are its safety—the topical agent induces only very mild erythema and has no systemic effects—and the fact that it treats not only visible AK lesions but also what he calls the "field cancerization"—the underlying dysplasia that gives rise to new AKs and eventually to skin cancers.

—Bruce Jancin