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Clinical Trials Highlights From ASCO's Annual Meeting

by Walter Alexander

While the vortex of media interest has funneled intensively toward angiostatin and endostatin, other angiogenesis agents are further along, both in development and in clinical assessment. Several among the class of matrix metalloproteinase inhibitors (MMPIs) are orally available, unlike angiostatin and endostatin, which must be administered parenterally because they are complex proteins.

At the 34th Annual Meeting of the American Society of Clinical Oncology, held in May 1998 in Los Angeles, Calif., Louise Grochow, M.D., associate professor of oncology, Johns Hopkins Oncology Center, Baltimore, Md., reported a trial of the MMPI BAY 12-9566 among twenty-seven patients (ages 37-77) with colorectal, breast, cervical, ovarian, and a variety of other solid tumors who had not responded to standard therapy. Grochow stated that after treatment with BAY 12-9566 fourteen patients had no tumor growth for at least four months, and five patients had none for seven to eleven months. The trial was designed to test whether inhibitory concentrations of the agent are clinically achievable. "Our target was 100 mgs per liter, but we got 50 percent greater than that," said Grochow. Changes in liver injury tests and mild thrombocytopenia at the highest doses were reversible after dose reduction.

The MMPIs, according to Karen Kumor, M.D., Bayer's international clinical project manager for BAY 12-9566, normally break down extracellular matrix to allow embryogenesis, vessel formation, and wound healing. Invading tumor cells induce surrounding matrix cells to produce the digestive proteases that break down structures and create room for the tumor mass to expand. The MMPIs interdict this process.

For more information about BAY 12-9566 (including information about ongoing clinical trials), call toll-free 888-442-4950.

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NSCLC AND A NOVEL COMBINATION THERAPY

Combining tirapazamine with cisplatin significantly prolongs survival in patients with advanced non-small cell lung cancer (NSCLC), according to Joachim von Pawel, M.D., Central Hospital, Gauting, Germany. Speaking for the International CATAPULT-1 (Cisplatin And Tirapazamine Against Previously Untreated Lung Tumors) Study Group, von Pawel said that under the hypoxic conditions found in most tumor cells, tirapazamine has two anti-tumor effects: hypoxic cytotoxicity and hypoxic sensitization. Normal tissues are not hypoxic to the same degree, and therefore little or no toxicity is expected from the agent.

The Phase III CATAPULT-I trial randomized 446 NSCLC patients (with stage IIIb or IV disease) to 390 mg/m^2 of IV tirapazamine over two hours, followed one hour later by 75 mg/m^2 of cisplatin (cis-Diamminedichloroplatinum) IV over one hour or 75 mg/m^2 cisplatin alone every three weeks for a maximum of eight cycles. Prophylactic antiemetics were administered as needed.

At a minimum of one-year follow-up, thirty-nine out of 119 patients were alive in the tirapazamine group as compared with twenty-five out of 119 in the control arm ($p=0.042$). Median survival was longer for the patients receiving the tirapazamine/cisplatin combination (34.6 weeks vs. 27.7 weeks) to a highly significant degree ($p=0.0078$) as compared with cisplatin alone. Among stage IV patients without brain metastasis, median survival was 36.6 weeks for the combination and 27.0 weeks for cisplatin alone.

Differences in response rates (27.5 percent vs. 13.7 percent for cisplatin) also favored the combination to a highly significant degree ($p<0.001$). Time to tumor progression was significantly longer for the combination therapy.

von Pawel reported that tirapazamine-related toxicity was mostly mild-to-moderate and included acute, reversible hearing loss (24 hours), incremental increases of nausea and vomiting, diarrhea, and skin rashes compared to cisplatin alone. Muscle-cramping was frequent, but manageable.

von Pawel concluded that tirapazamine prolongs survival when combined with cisplatin in patients with advanced NSCLC. The lack of additional myelosuppression may allow combinations with full doses of other myelosuppressive agents, he said.

COLORECTAL CANCER AND A NOVEL COMBINATION THERAPY

A trial of two thymidylate synthase inhibitors in outpatient treatment of advanced colorectal cancer (CRC) demonstrated both synergy and tolerability for the combination. A. Harstrick, M.D., Department of Internal Medicine, West German Cancer Center, Essen, Germany, noted that earlier Phase III trials of raltitrexed (Tomudex, Zeneca) versus the Mayo regimen of 5-fluorouracil (5-FU) and leucovorin among a total of 692 patients had shown response rates to be similar.

Based on that finding, Harstrick and co-investigators conducted a study combining raltitrexed given

every three weeks with a weekly 24-hour infusion of 5-FU. "What is important here is that we combined two classes of thymidylate synthase inhibitors and found that we could give almost full doses of both drugs, 2.4 g of 5-FU infusion and 2.63 mg/m^2 of raltitrexed every three weeks, without unexpected toxicity," Harstrick said in an interview. With sixteen of twenty-five advanced CRC patients now evaluable, significant anti-tumor activity is apparent, Hastrick observed. Partial responses have been noted in eight patients with the remaining showing disease stabilization or minor tumor regressions.

"With this newer regimen we may get up to a 30 percent response rate," he said, pointing out that the currently accepted response rate in this patient population is in the range of 25 percent.

Dose-limiting toxicities were found only at the highest dose, with one patient reporting grade III diarrhea and one patient with grade IV thrombocytopenia. Generally, Harstrick stated, the regimen has been well-tolerated.

BREAST CANCER AND CAPECITABINE TREATMENT

Experts agree that for heavily pretreated patients with metastatic breast cancer, the therapeutic goal is palliation. Joanne L. Blum, M.D., Ph.D., Texas Oncology, Dallas, Tex., presented data from a trial of capecitabine (Xeloda, Roche), an agent recently approved by the U.S. Food and Drug Administration for refractory metastatic breast cancer.

"Effective treatments without severe side effects for patients with metastatic breast cancers refractory to anthracyclines and taxanes are limited," Blum noted. Anti-tumor activity has been demonstrated for capecitabine, she noted, in a variety of cancers including breast, colorectal, gastric, and cervical cancer. Blum also said that experience in the recent trial suggests that capecitabine can be taken orally at home, making it unique among currently available salvage regimens for metastatic breast cancer.

Blum reported results of a trial conducted among 162 metastatic breast cancer patients whose disease had progressed despite prior treatment with two or three prior chemotherapeutic regimens (one of which contained paclitaxel). The median time from initial diagnosis to disease recurrence, Blum reported, had been 2.5 years. Repeated as a three-week cycle, the twice-daily oral capecitabine regimen totaling 2510 mg/m^2 per day was sustained for two weeks followed by a one-week rest period.

The median duration of response among the 135 patients with measurable disease was 241 days, and the median survival for the overall group was 384 days, Blum reported. Data analysis showed clinical response in twenty-seven patients (three complete responses and twenty-four partial responses) observed in visceral, soft tissue, and breast involvement sites. Disease remained stable for fifty-four patients (40 percent). "Sixty percent had responses or remained stable," Blum said, noting also that forty-six (34 percent) had progressive disease within the first six weeks of capecitabine treatment.

Blum reported that adverse events were easily managed with dose reductions. Seven percent of patients withdrew from treatment because of treatment-related events.

COLORECTAL CANCER AND OXALIPLATIN

European studies of the addition of oxaliplatin to a bimonthly schedule of leucovorin and 5-fluorouracil (5-FU) show some of the longest progression-free overall survival of any multicenter trial for patients with CRC, according to ASCO discussant Mace L. Rothenberg, M.D., associate professor of medicine, Vanderbilt University Medical Center, Nashville, Tenn. Oxaliplatin, he noted, appears to be substantially non-cross-resistant, demonstrating activity in tumors resistant to cisplatin.

The standard U.S. treatment for patients with advanced CRC has been the NCCTG (North Central Cancer Treatment Group)/Mayo regimen, one in which patients receive leucovorin and a bolus plus IV infusion of 5-FU over several hours as outpatients for five days every four to five weeks. However, efficacy superior to the standard NCCTG/Mayo Clinic regimen was demonstrated last year with a bimonthly regimen of leucovorin and a bolus plus IV infusion of 5-FU given over two days. Professor Aimery de Gramont, M.D., Hôpital Saint-Antoine, Paris, France, reported that both response rates and progression-free survival favored the bimonthly regimen, and it was clearly less toxic, avoiding the significant diarrhea and painful mucositis of the Mayo regimen.

In the new trial, patients (210 in each group) with unresectable metastases were randomized to the Mayo leucovorin/5-FU combination or to the bimonthly regimen with oxaliplatin added [leucovorin 200 mg/m^2/two-hour IV infusion followed by 5-FU 400 mg/m^2 bolus and 600 mg/m^2 IV infusion days one and two every two weeks, either with or without oxaliplatin 85 mg/m^2/two-hour IV infusion on day one].

Response rates were 51.2 percent for the regimen with oxaliplatin as compared with 22.6 percent for the regimen containing leucovorin and 5-FU. Progression-free survival was longer for the regimen including oxaliplatin (37.9 weeks vs. 26.4 weeks). In incomplete survival analysis, no overall survival benefit is apparent at this time, deGramont reported. That lack of survival, however, may be affected by the fact that about 20 percent of patients in the leucovorin/5-FU group with tumor progression had gone on to second-line treatment with the oxaliplatin-containing regimen. Overall, side effects were acceptable, de Gramont said.

A RESOURCE FOR PATIENTS WITH OVARIAN CANCER

Patients with ovarian cancer and their families have access to a comprehensive overview of ovarian cancer through the web site of Cancer Care, Inc. (www.cancercare.org). The web site features a section exclusively devoted to information about ovarian cancer, including tumor differentiation and staging, risk factors, and diagnostic and treatment options. Answers to common questions that patients with ovarian cancer have regarding their disease are also included.

The new section complements other sections on specific types of cancer such as breast, prostate, lung, colon, brain, and melanoma. Cancer Care, Inc., is a national nonprofit agency dedicated to providing emotional support, information, and practical help to people with cancer and their loved ones.

HARVESTING STEM CELLS

The Ireland Cancer Center and the University MacDonald Women's Hospital of University Hospitals of Cleveland in Cleveland, Ohio, are working together to train physicians and other medical professionals involved in childbirth to retrieve blood from the umbilical cord left behind after a baby has been successfully delivered.

The blood inside the cord contains valuable stem cells, which can be retrieved, frozen, and stored. These stem cells can later be transplanted into a cancer patient whose own bone marrow has been depleted after chemotherapy or radiation treatments. Though cord blood has been used sporadically since 1988 for transplantation into children suffering from leukemias and other blood disorders, the treatment is relatively new in adult patients. University Hospitals of Cleveland is one of three medical centers nationwide offering cord blood transplantation for adult cancer patients.

Expectant parents will be offered an opportunity to donate their newborn's umbilical cord as part of a university initiative to offer a new life-saving treatment option for cancer patients and others suffering from deadly blood disorders. For more information about umbilical cord donation, contact the Ireland Cancer Center Cancer Information Service at 1-800-641-2422.

CHILDREN'S ONCOLOGY CAMP

The Young Adult Conference (YAC) is an event organized by the Children's Oncology Camp Foundation to help young adults with cancer between the ages of 17 and 23 cope with their unique concerns. Like anyone their age, these individuals need to develop life skills, choose a career, and work on relationships with peers and family. These are serious challenges under normal circumstances, but for young patients with cancer, they have been complicated by illness—and compounded by issues such as fertility and insurability.

The 8-day YAC offers attendees an opportunity to participate in a wide range of informative activities that includes educational and motivational speakers, workshops and small group discussions, grief and loss groups, and question-and-answer sessions with medical experts. The conference, which takes place at the Foundation's Camp Māk-A-Dream in Gold Creek, Mont., offers both summer and winter sessions. Among the many recreational activities offered are swimming, horseback riding, sapphire mining, canoeing, and fly fishing. (Winter conferences include skiing, snowshoeing, dog sledding, and ice sculpture.)

The Children's Oncology Camp Foundation is a nonprofit 501(c)(3) organization. The Young Adult Conference is funded by private donations and grants from various businesses, foundations, and organizations and is offered to participants at no charge. However, transportation costs are not provided. For more information, please call the Children's Oncology Camp Foundation at 406-549-5987.

A RESOURCE FOR PATIENTS WITH PROSTATE CANCER

The *Prostate Cancer Resources Guide*, a comprehensive resource guide for prostate cancer patients, their families and friends, and health care professionals is available from the American Foundation for Urologic Disease (AFUD). The publication contains detailed facts and information about prostate cancer, as well as compilations of organizations, publications, and other information resources related to this common type of cancer.

Included in the resource guide are tips from prostate cancer survivors; questions that prostate cancer patients should ask their health care providers; information on insurance coverage issues; home health care advice; nutrition information; a compilation of information on support and advocacy organizations; and background on FDA and NCI resources and American Cancer Society programs aimed at prostate cancer patients.

The American Foundation for Urologic Disease is a nonprofit, patient-based organization dedicated to the prevention and cure of urologic disease through the expansion of research, education, public awareness, and advocacy. Copies of the Prostate Cancer Resource Guide are available for $5 each. Contact AFUD at 410-468-1800; Fax: 410-468-1808.