Nanoparticle Albumin-Bound Paclitaxel for Metastatic Breast Cancer

Speaker: William J. Gradishar, MD, Associate Professor of Medicine; Director, Breast Oncology; and Director, Fellowship Program, Division of Hematology/Oncology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

Data from a phase III clinical trial were analyzed to compare nanoparticle albumin-bound (nab) paclitaxel (Abraxane™, Abraxis Oncology, a division of American Pharmaceutical Partners, Inc.) with standard Cremophor®-based paclitaxel (CP) (Taxol®, Bristol-Myers Squibb) for the treatment of metastatic breast cancer. The results indicated that nab-paclitaxel was more efficacious and less costly than CP, yielding a dominant cost-effectiveness strategy, with the potential for generating significant cost savings for payers and providers.

In this randomized trial, the overall response rates were 33% for women taking nab-paclitaxel and 19% for those taking CP. The time to tumor progression was 21.9 weeks with nab-paclitaxel and 16.1 weeks with CP.

A decision-analytical model was constructed to evaluate the cost-effectiveness of this new therapeutic modality from the perspective of providers and payers. Measures included the following:

- premedication costs
- administration costs (e.g., nursing, tubing, and ancillary equipment)
- treatment-failure costs based on typical chemotherapy regimens
- toxicity management costs associated with taxane therapy, including standards of care, treatment patterns, and drug costs as well as frequency of grade 3 and 4 toxicities from agents

From these data, the investigators determined the cost-effectiveness ratios of treatments and the overall cost derivations.

With regard to cost derivations, no premedication costs were associated with nab-paclitaxel because no steroid premedication or granulocyte-colony stimulating factors were required. The premedication cost per patient receiving CP was $115.50. The cost of chemotherapy per patient was $85.86 for nab-paclitaxel and $311.75 for CP. The cost of managing grade 3 and 4 toxicities was $4,934.70 for nab-paclitaxel and $7,227.57 for CP. The difference was driven primarily by the incidence of neutropenia and leukopenia, and the cost of treatment failure was estimated to be $1,067.34 lower with nab-paclitaxel than with CP. Chemotherapy drug acquisition costs were not included because pricing for nab-paclitaxel was not available at the time of analysis.

As noted earlier, nab-paclitaxel was more effective, with patients having a median time of progression-free survival of 5.06 months in contrast to 3.72 months with CP. Because nab-paclitaxel was more effective and less expensive, incremental cost-effectiveness ratio calculations were not necessary.

Novel Chemotherapeutic Combination for Locally Advanced or Metastatic Breast Cancer

Speaker: Jose Baselga, MD, Chairman, Oncology Service, Hospital Vall d’Hebron, Barcelona, Spain.

The combination of temsirolimus (CCI-779, Wyeth Research), a novel targeted mTOR kinase inhibitor, and letrozole (Femara®, Novartis), a well-known aromatase inhibitor, was well tolerated and effective, when administered on a low-dose schedule, in the treatment of postmenopausal women with locally advanced or metastatic breast cancer. The synergistic effects of the two antitumor agents allowed for decreased doses with fewer adverse drug effects (ADEs).

Researchers enrolled 80 postmenopausal patients into a phase II, three-arm study designed to evaluate two separate doses and schedules of orally administered temsirolimus, combined with letrozole as first-line or second-line therapy, in order to determine its preliminary safety and efficacy, as meas-
ured by objective tumor response rates. The women were randomly selected, in a 1:1:1 ratio, to receive the following regimens:

- a high-dose schedule for oral temsirolimus 25 mg daily or oral temsirolimus 75 mg five days every two weeks plus oral letrozole 2.5 mg daily (six patients in each group)
- oral letrozole 2.5 mg daily alone (three patients)

Because temsirolimus toxicity resulted in a dose delay, a dose reduction, or discontinuation of the high doses of this agent, the protocols were amended. Doses were reduced to lower amounts of oral temsirolimus: 10 mg daily or 30 mg five days every three weeks along with oral letrozole 2.5 mg daily (22 patients and 19 patients, respectively) or oral letrozole 2.5 mg daily alone (24 patients).

The low-dose schedules were well tolerated, with few dose delays or reductions occurring. ADEs such as mucositis, asthenia, constipation, headache, rash, vasodilatation, and back pain were mainly grade 1 or 2. The preliminary best tumor response data supported the selection of the temsirolimus 30-mg intermittent dose in combination with letrozole. With this combination, the objective response rate was 26%, with one complete response, four partial responses, and disease progression in one patient.

In the group receiving the 10-mg daily dose of temsirolimus plus letrozole, the objective response rate was similar, at 23%, with five partial responses; however, disease progressed in four patients. The remainder of the patients have been in the study for too short a time to evaluate stable disease.

The efficacy of letrozole alone was as expected in this patient population, with an objective response rate of 30%, all partial responses.

**Chemotherapy and Radiation Therapy in Glioblastoma Multiforme**

**Speaker:** Roger Stupp, MD, Professor of Medicine and Director, Brain Tumor and Chest Oncology Clinic, Multidisciplinary Oncology Center, University of Lausanne Hospital, Vaudois, Lausanne, Switzerland.

The addition of temozolomide (Temodar®, Schering), a chemotherapeutic agent indicated for the treatment of anaplastic astrocytoma, to standard radiation therapy significantly improved both progression-free survival and overall survival in patients with glioblastoma multiforme, a fast-growing primary brain tumor that is difficult to treat.

A randomized phase III clinical trial was conducted in more than 80 institutions throughout Europe, Canada, and Australia. A total of 573 new patients with histologically proven disease were enrolled in the study; 286 patients were randomly assigned to standard radiation therapy of 60 gray (Gy) in 30 daily fractions of 2 Gy; 287 patients received the same radiation therapy and concomitant oral temozolomide 75 mg/m² daily for up to 42 days, followed by up to six cycles of adjuvant oral temozolomide 150 to 200 mg/m², daily for five days every 28 days. The primary endpoint was survival, with the aim of a 30% improvement.

At two years' follow-up, the median survival time was 15 months for patients treated with both temozolomide and radiation and 12 months for patients who received radiation therapy alone. Progression-free survival was 7.2 months in the chemotherapy-plus-radiation patients but five months in the radiation-only patients.

Both parameters improved significantly in patients receiving temozolomide plus radiation. It is noteworthy that the addition of chemotheraphy to radiation therapy more than doubled the chances that patients with glioblastoma multiforme would be alive for two years, in contrast to patients treated only with radiation therapy: 27% of patients receiving temozolomide plus radiation therapy and 10% of those receiving radiation therapy alone survived two years.

One key to the effectiveness of this new therapy is that temozolomide caused few side effects and it was well tolerated. Patients can take the drug every day during radiation treatment instead of once every eight weeks, the common dosing schedule for other chemotherapeutic agents.

**Anti–Epidermal Growth Factor Human Monoclonal Antibody in Advanced Non–Small Cell Lung Cancer**

**Speaker:** Jeffrey Crawford, MD, Professor of Medicine, Interim Director of Medical Oncology, and Director of Clinical Research, Duke Comprehensive Cancer Center, Duke University Medical Center, Durham, North Carolina.

In an interim analysis of a two-part phase II study, front-line therapy with panitumumab (Amgen/Abgenix), a fully human monoclonal antibody directed against the epidermal growth factor receptor (EGFr), was well tolerated when given with paclitaxel and carboplatin in patients with advanced non–small cell lung cancer (NSCLC). Results demonstrated encouraging response rates and enhanced survival outcomes in the small number of patients in the dose-finding part of this study.

In this first part of the study, 19 patients were enrolled into three groups. Six patients received panitumumab 1.0 mg/kg, seven patients received 2.0 mg/kg, and six patients received 2.5 mg weekly. The drug was administered for up to eight six-week cycles. Patients also received intravenous (IV) paclitaxel 200 mg/m² over three hours every three weeks and carboplatin to target the area under the curve (AUC) of 6 for up to six three-week cycles. Responses were evaluated at the end of the sixth week of each panitumumab cycle, and results were confirmed at least three weeks later or more.

Five of the 19 patients had objective responses, with one complete response and four partial responses; 12 patients experienced stabilization of disease; and two patients experienced disease progression. The observed duration of response to date was six months, and the median overall survival was 17 months, a notably greater survival than with chemotherapy alone in patients with advanced NSCLC.

As noted, panitumumab at all three doses was safe in combination with paclitaxel and carboplatin. The most common ADE observed was skin rash, but the incidence of grade 3 rash did not increase with the dose.

Part 2 of this study is designed to confirm these findings and to compare the time to progression with panitumumab plus chemotherapy versus chemotherapy alone as front-line therapy for patients with advanced NSCLC. Enrollment has been
New Chemotherapeutic Combination for Advanced Pancreatic Cancer

Speaker: Christophe Louvet, MD, Professor of Medicine and Deputy Director, Oncology Department, Saint Antoine Hospital and University, Paris, France.

The combination of gemcitabine (Gem) (Gemzar®, Eli Lilly) and oxaliplatin (Ox) (Elotatin\textsuperscript{TM}, Sanoft-Synthelabo) significantly improves the treatment outcomes of advanced pancreatic cancer, compared with gemcitabine alone, particularly in response rates, clinical benefits, and progression-free survival.

A French and Italian intergroup, phase III clinical trial compared the efficacy and safety of gemcitabine and oxaliplatin with standard treatment consisting of gemcitabine alone in patients with nonresectable locally advanced or metastatic pancreatic cancer. A total of 313 patients were randomly assigned to receive gemcitabine 1 g/m\textsuperscript{2} in a two-hour IV infusion on the second day (GemOx) every two weeks or gemcitabine alone.

A final analysis of the data confirmed significantly improved overall response rates with the GemOx combination (28.7%) compared with gemcitabine alone (16.7%). Median progression-free survival was 5.5 months with GemOx and 3.7 months with gemcitabine. The clinical benefit response rates were 38.9% in the GemOx group and 29.2% in the gemcitabine-alone group, with both parameters significantly improved in the GemOx arm of the study.

Overall survival, although not statistically significant, was better than had been expected in both arms of the study: 7.1 months for the gemcitabine patients and 9.0 months for the GemOx patients. The projected survival for each arm had been six and eight months, respectively.

Oral Fluoropyrimidine for Metastatic Colon Cancer

Speaker: Joseph J. McKendrick, MD, Director of Medical Oncology, Department of Clinical Hematology and Clinical Oncology, Box Hill Hospital, Melbourne, Victoria, Australia.

Adjuvant chemotherapy with oral capecitabine (Xeloda\textsuperscript{®}, Roche), an oral fluoropyrimidine preferentially activated to 5-fluorouracil (5-FU) in tumors by enzymatic action, was more cost-effective than the standard Mayo Clinic regimen of IV 5-FU and leucovorin (LV) in the adjuvant treatment of metastatic colon cancer.

Medical resource utilization (MRU) data were evaluated from the Xeloda in Adjuvant Colon Cancer Therapy (X-ACT) study, a large, phase III randomized clinical trial that compared capecitabine and the Mayo Clinic regimen as adjuvant treatment for patients with stage III colon cancer. A total of 1,987 patients with metastatic colorectal cancer were randomly assigned to receive 24 weeks of treatment with either oral capecitabine 1,250 mg/m\textsuperscript{2} twice daily on the first to 14th days (e.g., antidiarrheal agents, analgesics, and antifungal agents) were necessary. Patients receiving capecitabine took more generic drugs (e.g., calcium supplements, low-cost vitamins and emollients).

Finally, patients both younger and older than 65 years of age tolerated treatment with capecitabine quite well. Both age groups experienced a similar low incidence of severe toxicities. This finding was important because colon cancer is most often diagnosed in older patients, who generally do not receive optimal treatment for this disease.

Overall, adjuvant chemotherapy for stage III colon cancer with oral capecitabine yielded substantial savings in MRU because the administrative costs of IV therapy could be avoided and because of substantial indirect cost savings in terms of patient time saved. The added value of equivalent disease-free survival and superior relapse-free survival rates make oral capecitabine a cost-effective alternative to the Mayo Clinic regimen, the present standard of care for the adjuvant treatment of stage III colon cancer.

Taxane-Based Chemotherapy in Hormone-Refractory Prostate Cancer

Speaker: Mario Eisenberger, MD, R. Dale Hughes Professor of Oncology and Urology, Johns Hopkins Kimmel Cancer Center, Baltimore, Maryland.

Docetaxel (Taxotere\textsuperscript{®}, Aventis), a well-known taxane chemotherapeutic agent for patients with metastatic breast cancer, provided a significant survival benefit when administered to patients with hormone-resistant prostate cancer, and it reduced the chance of dying by 24% while offering markedly improved quality of life.

The researchers randomly assigned 1,006 patients to receive docetaxel 30 mg/m\textsuperscript{2} weekly, docetaxel 75 mg/m\textsuperscript{2} once every three weeks, or mitoxantrone (Novantrone\textsuperscript{®}, Immunex) 12 mg/m\textsuperscript{2} once every three weeks. All of the patients also received 5 mg of oral prednisone daily. (The latter approach is the established standard of care as initial treatment to relieve pain in patients with advanced hormone-refractory cancer.)

The planned duration for all three arms was 30 weeks, and the primary study endpoint was survival. Secondary endpoints included pain response, measurable tumor responses, a decline in prostate-specific antigen (PSA) values, and improved quality of life over baseline measures.

At a median follow-up of 20.7 months, the men receiving higher-dose docetaxel every three weeks had a survival rate...
of 18.9 months; those receiving low-dose docetaxel weekly survived for 17.4 months; and those receiving mitoxantrone plus prednisone survived for 16.5 months. On average, therefore, patients who received higher-dose docetaxel every three weeks survived 2.4 months longer than those receiving mitoxantrone.

For the men who received higher-dose docetaxel every three weeks, PSA levels declined by 45%; for the patients receiving the lower dose of docetaxel, the levels were reduced by 48%; and for those receiving mitoxantrone plus prednisone, the levels were decreased by 32%.

Of equal importance, more men who received higher-dose docetaxel every three weeks experienced significantly greater pain relief (35%) than men who received low-dose docetaxel (31%) or mitoxantrone plus prednisone (22%) every three weeks.

Finally, the docetaxel patients experienced marked improvement in quality of life over baseline values compared with patients taking mitoxantrone. These improvements were observed in 22% of patients on the docetaxel three-times-weekly arm, in 23% on the docetaxel once-weekly arm, and in 13% of the men on the mitoxantrone and prednisone regimen.

**Oral Drug Combination for Multiple Myeloma**

**Speaker:** Vincent Rajkumar, MD, Hematologist, Mayo Clinic, Rochester, Minnesota.

Patients with newly diagnosed multiple myeloma responded better to treatment with the oral drug combination of thalidomide (Thalomid®, Celgene) plus dexamethasone (Decadron®, Merck) (thal/dex) than to dexamethasone therapy alone.

In a phase III clinical trial, coordinated by the Eastern Cooperative Oncology Group (ECOG), 207 patients were randomly assigned to take oral thalidomide 200 mg/day with oral dexamethasone 40 mg/day on the first to fourth days, the ninth to 12th days, and the 17th to 20th days or to take dexamethasone alone on the same schedule. Therapy was repeated monthly for four cycles.

Response to treatment was defined as a 50% or greater decrease in serum and urine mononclonal M-proteins, known indicators of tumor burden. In patients whose serum levels of M-protein were not measurable, a 90% or higher decrease in the urine M-protein was required.

The best response within four cycles of treatment was 58 of 98 patients receiving thal/dex, or 59%, versus 40 of 98 patients on dexamethasone alone, or 41%. These results suggest that this oral regimen can help bring multiple myeloma under good control and can prepare these patients for undergoing stem cell transplantation, a standard treatment used to stop the disease and prolong life.

The side-effect profile with thal/dex, however, was considerably greater than that seen with dexamethasone alone; 44% of patients in the thal/dex arm of the study had serious ADEs, compared with 19% receiving dexamethasone alone. The fact that deep vein thrombosis occurred in 16% of patients receiving thal/dex, but in only 3% of patients treated with dexamethasone alone, points to the need for anticoagulants to be given initially to prevent these blood clots.

On the basis of the promising results of thal/dex and dexamethasone in this study, it appears that this oral regimen might provide an effective alternative for complex IV chemotherapy such as vincristine/adriamycin/dexamethasone (VAD) as first-line treatment for multiple myeloma. Physicians might consider dexamethasone alone for low-risk patients and thal/dex for patients with more aggressive disease necessitating immediate tumor reduction.

**Darbepoetin alfa for Anemia of Cancer**

**Speaker:** Venna Charu, MD, Community Oncologist, Pacific Cancer Medical Center, Anaheim, California.

Results from a multicenter study indicated that darbepoetin alfa (Aranesp®, Amgen) was effective in treating anemia in cancer patients who were not receiving concurrent chemotherapy.

More than a quarter of a million cancer patients experience anemia of cancer annually. Investigators conducted a multicenter, randomized, comparative, open-label, 25-week study to estimate the difference in the number of hospitalization days over 12 weeks in patients with anemia of cancer treated with darbepoetin alfa and in patients not receiving treatment. The study also aimed to compare the efficacy and safety of darbepoetin alfa versus no treatment.

Patients were randomly selected to receive darbepoetin alfa 3 mcg/kg every two weeks for 21 weeks, with a dose increase permitted or a control observation for 12 weeks. This step was followed by optional treatment with darbepoetin alfa 3 mcg/kg every two weeks for nine weeks, with a dose increase permitted.

Although the planned sample size was 1,000 patients, a total of 285 patients were enrolled, in a 4:1 ratio; 226 were assigned to the darbepoetin alfa group and 59 were assigned to the control group. At this point, study enrollment was terminated.

Patients were permitted to receive transfusions at the treating physician’s discretion. A Subjects Outcomes Questionnaire was administered at the baseline evaluation and every four weeks through the end of the study. All patients returned for a follow-up visit four weeks after receiving the last dose of the study drug.

Hospitalization results were comparable for treated and control patients. The number of patients hospitalized was similar, and the length of hospital stay was equivalent. However, these results were not conclusive because the target sample size of 1,000 patients was not reached.

The incidence of red blood cell transfusions was significantly lower for the darbepoetin alfa patients than for the controls during the fifth to 12th weeks, with transfusions being required in 8% of patients taking darbepoetin alfa and in 22% of the patients in the control group.

Patients taking darbepoetin alfa experienced a significant reduction in fatigue and mean change in hemoglobin over time that was significantly greater than in the controls. Patients in the control group who elected to receive darbepoetin alfa after 13 weeks of observation experience a substantial increase in mean change in hemoglobin during weeks 13 to 21.