Effect of Octreotide (Sandostatin LAR) For Neuroendocrine Midgut Tumors: The PROMID Trial

- Rudolf Arnold, MD, Professor of Medicine, Philipps University, Marburg, Germany
- Discussant: James C. Yao, MD, MD Anderson Cancer Center, Houston, Tex.

Long-acting-release octreotide acetate injection (Sandostatin LAR, Novartis) at a dose of 30 mg significantly prolonged the time to tumor progression in patients with midgut neuroendocrine tumors (NETs) and showed particular benefit among patients with a low tumor burden. (Octreotide is a synthetic version of the hormone somatostatin.) Although in vitro and in vivo studies have shown antiproliferative effects of octreotide in NETs with tumor stabilization and partial regression in some patients, the in vivo studies, among other drawbacks, had heterogenous populations and were not placebo-controlled.

PROMID (Placebo-controlled prospective Randomized study on the antiproliferative efficacy of Octreotide LAR in patients with metastatic neuroendocrine MIDgut tumors) was a double-blind phase 3b study that aimed to include 162 treatment-naïve patients with histologically confirmed locally inoperable or metastasized well-differentiated NETs of the midgut. Patients were assigned to receive either octreotide LAR 30 mg/month or placebo for 18 months or until tumor progression or death. The primary endpoint was the median time to tumor progression.

At a planned interim analysis with 85 evaluable patients (median age, 62 years), the time to tumor progression was 15.6 months for octreotide LAR and 5.9 months for placebo (hazard ratio [HR], 0.33; \( P = 0.000017 \)). At six months, partial responses were reported in one octreotide patient and in one placebo patient; stable disease was reported in 28 octreotide patients and in 16 placebo patients; and progressive disease was reported in 10 octreotide patients and in 23 placebo patients. The benefits of octreotide LAR 30 mg over placebo were observed whether or not the NETs were functioning (i.e., secreting hormones). In patients with a hepatic tumor load of 10% or less, the median time to tumor progression was 28.78 months with octreotide LAR and 6.14 months with placebo. In patients with a tumor burden above 10%, the median time to tumor progression was 10.35 months with octreotide LAR and 4.48 months with placebo.

Five of 42 octreotide LAR patients discontinued treatment, usually because of gastrointestinal (GI) adverse events.

Dr. Arnold concluded, “Octreotide LAR should be considered the standard of care in patients with well-differentiated midgut NETs.”

Dr. Yao, while acknowledging the benefits of octreotide LAR in the time to tumor progression in PROMID, said that because of a range of yet-unanswered questions, he could only go so far as to suggest that octreotide LAR 30 mg every four weeks can be considered an acceptable therapeutic option in this population.

Comparison of Cisplatin/S-1 Tablets With Cisplatin/5-FU Infusions For Advanced Gastric Cancer: The FLAGS Trial

- Jaffer Ajani, MD, Professor of Medicine, Department of Gastrointestinal Oncology, MD Anderson Cancer Center, Houston, Tex.

The standard therapy for advanced gastric cancer—cisplatin (Platinol, Bristol-Myers Squibb) plus 5-fluorouracil (5-FU)—is inconvenient because of the protracted 5-FU infusion. In the multicenter, phase 3 FLAGS trial (First-Line Advanced Gastric Cancer Study), 5-FU was replaced with S-1, a tablet that allowed more convenient administration and fewer office visits. FLAGS was supported by Taiho Pharma.

In this study, 1,053 patients with untreated, advanced gastric or gastroesophageal adenocarcinoma were randomly assigned to receive first-line S-1 at a dose of 25 mg/m² twice daily on days 1 to 21 plus cisplatin 75 mg/m² on day 1, then every 28 days, or 5-FU 1,000 mg/m² per day of a five-day infusion plus cisplatin 100 mg/m² on day 1, then every 28 days. The primary endpoint was overall survival. Results were stratified according to diffuse or non-diffuse histological findings. The diffuse histological type was by far the most common (in approximately 68% of patients).

Median overall survival was longer with cisplatin/S-1 (8.6 months), but not to a significant extent, compared with 7.9 months for cisplatin plus 5-FU (\( P = 0.1983 \)).

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MEETING HIGHLIGHTS: American Society of Clinical Oncology

Grade 3 and 4 hematological adverse events (AEs), however, were significantly higher in patients receiving cisplatin/5-FU, with increases in neutropenia, thrombocytopenia, leukopenia, and febrile neutropenia (P < 0.01 for each of the preceding). Among nonhematological AEs, hypokalemia, stomatitis, mucosal inflammation, and hypophosphatemia (P < 0.01 for all), as well as hypomagnesemia (P < 0.05), were higher with cisplatin plus 5-FU.

Dr. Ajani commented: “Kidney abnormalities were more common with 5-FU, and liver [abnormalities were more common] with cisplatin/S-1. But if you look at the whole picture, it clearly favors cisplatin/S-1.”

A post hoc non-inferiority analysis showed that mortality risk with cisplatin/S-1 fell well within stringent (HR = 1.10) non-inferiority (HR = 0.92) boundaries (P = 0.0068). In the analysis, median overall survival was nine months for the diffuse histological type and 8.3 months for the non-diffuse histological type (P = 0.04).

Dr. Ajani concluded: “This finding is not definitive, but it is hypothesis-generating and we need to study it further. Cisplatin/S-1 is an optimum substitute for cisplatin/5-FU in the treatment of advanced gastric cancer.”

Dasatinib (Sprycel) for Chronic-Phase Chronic Myeloid Leukemia (Three-Year Follow-up)
• Richard M. Stone, MD, Dana-Farber Cancer Institute, Boston, Mass.

In a three-year follow-up evaluation of the 139-center, open-label, phase 3 trial (CA 180034) of chronic myeloid leukemia–chronic phase (CML–CP), the most favorable long-term benefit–risk profile was demonstrated for dasatinib (Sprycel, Bristol-Myers Squibb) at a dose of 100 mg once daily. An FDA-approved agent, dasatinib is a short-acting oral tyrosine kinase inhibitor. Four dasatinib arms were included: 165 patients received the 100-mg dose once daily; 167 patients received 70 mg twice daily, 163 patients received 140 mg once daily, and 167 patients received 50 mg twice daily. All of the patients had experienced drug resistance, suboptimal responses, or intolerance to prior treatment with imatinib (Gleevec, Novartis). The trial’s objective was to evaluate the long-term efficacy and tolerability of dasatinib 100 mg once daily and the predictive value of cytogenetic and molecular responses at 12 months. The minimum follow-up period was 36 months.

With dasatinib 100 mg once daily, the three-year progression-free survival rate was 73%, and the overall survival rate was 87%. Progression-free survival was similar regardless of the patient’s baseline bcr-abl mutation status.

Progression-free survival was 67% with dasatinib 70 mg twice daily, 60% for 140 mg once daily, and 72% for 50 mg twice daily. Overall survival was 80% with dasatinib 70 mg twice daily, 84% with 70 mg twice daily or 140 mg twice daily, and 84% with 50 mg twice daily.

Among patients with any baseline bcr-abl mutation and resistance or suboptimal response to imatinib, progression-free survival was 66% for dasatinib 100 mg once daily, compared with 45% to 57% for the other doses.

A landmark analysis confirmed that responses to dasatinib 100 mg once daily at 12 months were predictive of progression-free survival at 36 months. For patients with major molecular or complete cytogenetic responses at 12 months, progression-free survival was 92% to 93%. For patients with other or no cytogenetic responses, progression-free survival was 63%. For patients with partial cytogenetic responses at 12 months, progression-free survival was 77%.

In general, dasatinib 100 mg once daily was the better-tolerated dose, with few grade 3 or 4 AEs occurring between 24 and 36 months of follow-up.

Dr. Stone concluded, “Dasatinib 100 mg once-daily offers a more favorable long-term benefit–risk profile in this population of CML–CP patients following resistance, suboptimal response, or intolerance to prior imatinib.”

Ipilimumab for Advanced Melanoma: 18-Month Update (487 Patients)
• Stephen O’Day, MD, Chief of Research and Director, Melanoma Program, Angeles Clinic and Research Institute, Santa Monica, Calif.

In three pivotal phase 2 studies (CA 184008, CA 184022, and CA 184007), 487 patients with advanced melanoma receiving ipilimumab 10 mg/kg had comparatively high long-term survival rates. Also known as MDX-010 or MDX-101 (Bristol-Myers Squibb/Medarex), ipilimumab is a fully human monoclonal antibody that targets cytotoxic T-lymphocyte antigen-4 (CTLA-4) and potentiates antitumor immune responses.

Patients received ipilimumab every three weeks for four cycles. Eligible patients could continue to receive maintenance doses of ipilimumab every 12 weeks from week 24 onward in each of the studies. All three trials enrolled patients with unresectable stage III or IV melanoma. Only the CA 184007 trial enrolled previously treated patients (n = 53). The median follow-up evaluation ranged from 10.1 to 16.3 months. The study objective was to provide updated survival data for 37.5 months of follow-up or less.

Twelve-month overall survival rates exceeded 47%, 18-month overall survival rates exceeded 34 months, and 24-month overall survival rates exceeded 30%. For the three trials, median survival times were 10.2 months in CA 184008, 11.4 months in CA 184022, and 19.3 months in CA 184007. Median survival was 17.7 months for the 58 patients receiving ipilimumab plus budesonide (AstraZeneca) in CA 184007.

Among previously treated patients, 24-month survival rates ranged from 24% to 33%. In all three studies, a “meaningful proportion of patients continue to survive beyond the follow-up period,” Dr. O’Day said in an interview. He said also that survival is about 10% with interleukin-2 (IL-2) and that melanoma in many of the patients was refractory to IL-2.

The considerable number of immune-related toxicities experienced with ipilimumab (diarrhea, rash, pituitary abnormalities, and liver abnormalities) were manageable with steroids when they were severe. These AEs also seemed to correlate with long-term benefit, Dr. O’Day commented.

He added: “This is encouraging. It suggests that with this class of drugs, while the response rate may be fairly low, the survival curves show a plateau above 30%.”

Ipilimumab is currently being investigated in a phase 3 melanoma trial.
Ipiilimumab for Advanced Melanoma (287 Patients)
• Jose Lutzky, MD, Director, Melanoma Program, Mount Sinai Hospital, Miami, Fla.

Although rates of disease control and survival have been associated with immune-related AEs among ipilimumab-treated patients with advanced melanoma, benefits are also observed among those who do not go on to experience these events.

Patients with unresectable stage III or IV melanoma (n = 287) were enrolled in three completed phase 2 studies (CA 184008, CA 184022, and CA 184007). They received ipilimumab 10 mg/kg every three weeks for four cycles. Eligible patients could continue to receive maintenance doses of ipilimumab every 12 weeks from week 24 onward.

Immune-related AEs of grade 2 or higher were reported in 39.4% to 64.9% of patients in the three studies, with total AE rates ranging from 70.4% to 84.2%. The most common immune-related AEs were colitis, rash, autoimmune hepatitis, and uveitis. Immune-related colitis can be severe and life-threatening, Dr. Lutzky said.

In patients with grade 0 or grade 1 level events, disease control (defined as a complete response plus a partial response plus stable disease, according to modified WHO criteria) was present at a rate of 20% to 24%. The disease control rate was higher among those who experienced AEs, compared with those who did not, but the difference in disease control rates between grade 0/1 versus grade 2 or higher AEs was not statistically significant.

Median overall survival was also correlated with immune-related AEs. In studies CA 184008 and CA 184022, among patients who lived up to day 81, median overall survival from day 81 in patients with any immune-related AEs was 14.8 months, compared with 8.21 months for patients with no immune-related AEs within 12 weeks. Among patients with any grade 2 level or higher immune-related AEs, median overall survival was 13.6 months, compared with 11.3 months for those without immune-related AEs.

“We try to treat these events and keep patients on treatment, because these are the patients who tend to do the best,” Dr. Lutzky said.

Although the data confirm that it is likely that immune-related AEs are associated with ipilimumab’s mechanism of action, Dr. Lutzky emphasized that many responses occurred in patients with no immune-related AEs after 12 weeks of treatment.

“The take-home message is that if a patient has an immune action, that is encouraging, but if they don’t, it’s not discouraging.”

Ixabepilone/Bevacizumab versus Paclitaxel/Bevacizumab for Metastatic Breast Cancer
• Hope Rugo, MD, Professor of Medicine, University of California, San Francisco, Calif.

In human colon, breast, lung, and renal carcinoma xenograft models, the combination of ixabepilone (Ixempra, Bristol-Myers Squibb) and bevacizumab (Avastin, Genentech) demonstrated greater therapeutic synergism than a standard of care—the combination of paclitaxel (Taxol, Bristol-Myers Squibb) and bevacizumab. A randomized phase 2 trial of either weekly or every-three-week schedules of ixabepilone plus bevacizumab in patients with metastatic breast cancer showed encouraging activity compared with weekly paclitaxel plus bevacizumab, with similar overall safety profiles. As the first epothilone approved for the treatment of breast cancer, ixabepilone is a microtubule-stabilizing agent.

The trial’s primary endpoint was to compare objective response rates of ixabepilone/bevacizumab given weekly or every three weeks with paclitaxel/bevacizumab as a first-line therapy for 122 women with advanced breast cancer. The women (median age, approximately 59 years) had measurable disease and no prior chemotherapy for locally advanced or metastatic breast cancer. These patients were randomly assigned to receive the following intravenous (IV) doses, in a 3:2:2 fashion:
- ixabepilone 16 mg/m² IV on days 1, 8, and 15 every 28 days plus bevacizumab 10 mg/kg IV every two weeks
- ixabepilone 40 mg/m² IV every three weeks plus bevacizumab 15 mg/kg IV every three weeks
- paclitaxel 90 mg/m² IV plus bevacizumab 10 mg/kg IV every two weeks

Treatment was continued until disease progression or until unacceptable toxicity.

For the weekly and every-three-week ixabepilone-containing arms, overall response rates were 75% and 86%, respectively. For the paclitaxel/bevacizumab arm, the overall response rate was 56%.

Grade 3 and 4 neutropenia was reported in 11.1% of women in the weekly ixabepilone arm, in 54.8% in the every-three-week ixabepilone arm, and in 21.9% of the paclitaxel-containing arm. It is notable that febrile neutropenia occurred rarely, at the rate of 2.2% for the every-three-week ixabepilone/bevacizumab arm and at 0% for the other two arms.

Dr. Rugo described the ixabepilone/bevacizumab activity in the first-line treatment of metastatic breast cancer as “encouraging,” but she pointed forward to final results that are expected to be available in a year and to large-scale cooperative group trials currently enrolling patients.

She concluded: “Ultimately, we hope this will get us closer to individualizing therapy for specific biologic criteria in the tumor that could allow us to treat patients with more effective regimens up front.”

Effects of Letrozole (Femara) and Tamoxifen (Nolvadex) on Cognitive Function In Postmenopausal Breast Cancer (BIG 1-98)
• Karen Ribi, PhD, International Breast Cancer Study Group, Bern, Switzerland.

Cognitive dysfunction has been recognized as a potential long-term adverse effect of adjuvant chemotherapy for breast cancer. A cognitive substudy of the BIG 1-98 clinical trial (Breast International Group 1-98) among postmenopausal women with hormone receptor–positive, early-stage breast cancer found better cognitive function among those receiving letrozole...
(Femara, Novartis) during the last three of five years of treatment than among those receiving tamoxifen citrate (Nolvadex, AstraZeneca).

Women in BIG I-98 (n = 120; mean age, 64.5 years) were randomly assigned to receive adjuvant endocrine treatment consisting of one of these regimens:

- tamoxifen for five years
- letrozole for five years
- tamoxifen for two years, followed by letrozole for three years
- letrozole for two years, followed by tamoxifen for three years

During the fifth year of treatment, investigators used computerized tests to evaluate components of objective cognitive function (speed of psychomotor function, visual attention, working and verbal memory, and learning). Assessment of cognitive measures among the women, while showing only one cognitive domain component (visual attention) to favor letrozole significantly ($P = 0.05$), did reveal a significant advantage for letrozole in the composite score, the substudy primary endpoint ($P = 0.04$). Although cognitive impairment (defined as $z$ scores higher than 1.96 standard deviations below the norm) was demonstrated with both drugs for all cognitive tasks, the greatest difference appeared for memory, which was impaired by 6.2% among patients receiving letrozole and by 25.5% for those receiving tamoxifen ($P = 0.003$).

In an interview, Dr. Ribi said: “It was expected that because of the estrogen deprivation associated with aromatase inhibitors, patients who received letrozole would have worse cognitive function compared to those who received tamoxifen. These substudy findings do refute our initial hypothesis and show better cognitive function for patients taking letrozole.”

### Patupilone for Ovarian, Fallopian, or Peritoneal Cancer Refractory or Resistant to Platinum Therapy

- Willem M. Smit, MD, Medisch Spectrum Twente, Enschede, Netherlands

Patupilone (epothilone B, EPO906) showed promising activity in patients with recurrent ovarian cancer that was platinum-refractory and platinum-resistant. Administered at a dose of 10 mg/m² every three weeks, patupilone was safe and well tolerated in a phase 2 open-label clinical trial. Patupilone, a natural epothilone isolated from a myxobacterium (a soil bacterium), is a microtubule-targeting cytotoxic agent.

Patients with ovarian cancer that relapses or recurs within six months after platinum plus taxane therapy have a poor prognosis. The primary objective of the study, which included 112 women (median age, 56 years) with documented platinum-refractory or resistant progressive ovarian, primary fallopian, or primary peritoneal cancer, evaluated best overall response. Participants had received up to three prior therapies, including platinum plus a taxane. The primary site was ovarian in 93% of women, with most cancers (68.8%) classified as stage III at the initial diagnosis. Nearly 50% of the patients had tumors that progressed within three months of their last platinum treatment.

Among the 97 women with measurable disease at baseline, partial responses were reported in 7.1% of the patients, stable disease in 45%, and progressive disease in 35.7%. Best overall response, consisting of a complete response plus a partial response, was 7.1%. The median duration of disease control (defined as a complete response plus a partial response plus stable disease) was 4.2 months. Median overall survival was 11.2 months, with a one-year overall survival rate of 47.5%.

Among five deaths reported, none was attributed to patupilone. Diarrhea, the most common AE (in 53.6% of patients; grade 3 and 4 in 24.1%), was manageable and of short duration. Nausea was reported in 44.6% of patients (grade 3 and 4 in 3.6%) and vomiting in 28.6% of patients (grade 3 and 4 in 3.6%). Neuropathy was primarily grade 1. No hematological toxicity, myelosuppression, hepatic or cardiac toxicity, or hypersensitivity was reported.

Dr. Smit concluded: “Patupilone showed promising activity in a platinum-refractory/resistant population.”

A large phase 3 trial of more than 800 patients with platinum-refractory and platinum-resistant, recurrent ovarian cancer is ongoing.