Endocrine Therapy plus Zoledronic Acid (Zometa) And Breast Cancer Recurrence

- Michael Gnant, MD, Medical University of Vienna, Vienna, Austria

In what was surely one of the most striking findings of the entire conference, zoledronic acid (Zometa, Novartis) 4 mg, given every six months, significantly improved clinical outcomes among women with endocrine-responsive early breast cancer in the Austrian Breast Cancer Study Group-12 (ABCSG) Trial. The implication, stated Dr. Gnant, “is that a low- and intermediate-risk patient subgroup can be spared the side effects of cytotoxic therapy after locoregional treatment.”

The trial’s intent was to determine whether treatment with surgery plus goserelin acetate (Zoladex, AstraZeneca) could prevent recurrence in premenopausal women with early-stage breast cancer. The researchers randomly assigned 1,803 women (median age, 45 years) to receive either tamoxifen (Nolvadex) or anastrozole (Arimidex), both made by AstraZeneca, to compare the two endocrine suppressive agents.

After the patients underwent surgery and radiation, they received goserelin 3.6 mg every 28 days; they were then randomly assigned to receive tamoxifen 20 mg/day or anastrozole 1 mg/day. The primary endpoint was disease-free survival.

After a median follow-up of 60 months, Dr. Gnant said, no treatment differences were found with either drug in this component of the trial. Disease-free survival of at least five years was reported for 94% of women, and five-year overall survival was observed for 98.2%.

Differences did appear, however, in a sub-randomization study in which half of each treatment group also received zoledronic acid. For the women receiving zoledronic acid 4 mg every six months, about 94% achieved five-year progression-free survival, compared with 91% of patients not receiving the bisphosphonate. The 3% absolute difference translated to a relative risk reduction of about 35% ($P = 0.10$), with 16 deaths, compared with 26 deaths in the group not given zoledronic acid. Other reductions in contralateral breast cancer and in distant non-bone metastases were reported with zoledronic acid.

The combination of adjuvant endocrine therapy and zoledronic acid therapy was well tolerated, without incidence of osteonecrosis of the jaw or renal toxicity, Dr. Gnant said. He concluded, “Zoledronic acid significantly improves clinical outcomes beyond those achieved with endocrine therapy alone.”

Everolimus (RAD001) in Renal Cell Carcinoma

- Robert Motzer, MD, Memorial Sloan-Kettering Cancer Center, New York, N.Y.

Everolimus, an investigational therapy, prolonged progression-free survival in renal cell carcinoma (RCC) patients whose disease had progressed while they were receiving vascular endothelial growth factor receptor (VEGF-R)/tyrosine kinase inhibitor (TKI) therapy with sunitinib (Sutent, Pfizer), sorafenib (Nexavar, Bayer), or both. Everolimus targets mTOR (mammalian target of rapamycin) protein, a central regulator of tumor cell division, cell metabolism, and angiogenesis. The phase 3 clinical trial finding was reported by Dr. Motzer.

The trial included 410 patients falling within Sloan-Kettering’s risk-stratification groups of “favorable,” “intermediate,” or “poor,” who were randomly assigned to receive oral everolimus 10 mg/day plus best supportive care (n = 272) or placebo plus best supportive care (n = 138). Median age was 60 years. In both groups, 94% of patients had two or more metastatic sites. Each patient had previously been treated with other agents: 71% with sunitinib, 55% with sorafenib, and 26% with both. The primary endpoint was progression-free survival.

After the second interim analysis, the Independent Monitoring Committee recommended termination of the study’s placebo arm; these patients were offered treatment with everolimus. Median progression-free survival was four months for the everolimus patients and 1.9 months in the placebo group (HR = 0.30, $P < 0.001$). Progression-free survival was 4.8 months for everolimus and 1.8 months for placebo; at six months, the progression-free survival rate was 20% for the everolimus patients and 2% for the placebo patients. The benefits of this agent were reported for all subgroups according to their risk; the TKI agent used; and the patient’s age, sex, and geographic region. Median overall survival, which had not been reached in the everolimus group, was 8.8 months with placebo (HR = 0.83, $P = 0.23$).

Everolimus was generally well tolerated; 10% of patients discontinued treatment because of adverse events, compared with 4% who withdrew in the placebo group. Stomatitis was the most common event (in 36%), but grade 3 and 4 events were the most common event (in 36%), but grade 3 and 4 events were
reported in only 4% of patients.

Dr. Motzer concluded, “Everolimus is the first and only agent with established benefit for the treatment of patients with renal cell carcinoma after VEGF-R/TKI therapy. It should be the standard of care in this setting, pending approval.”

Dr. Rini, an ASCO discussant, noted that given the absence of a real standard of care in this setting, the findings are of particular importance. “Everolimus significantly prolongs progression-free survival versus placebo across risk groups in TKI-refractory renal cell carcinoma,” he said, adding that prospective translational and clinical investigation is needed to define the most appropriate sequence of therapies.

Ixabepilone (Ixempra) and Renal Cell Cancer

Hui Huang, MD, National Cancer Institute, Bethesda, Md.

In a further clinical trial of therapy for RCC, ixabepilone (Ixempra, Bristol-Myers Squibb) demonstrated a two-fold reduction in the growth rate constant and a correlation of that rate with overall survival in patients with metastatic RCC (mRCC). Approved in 2007 for the treatment-resistant metastatic breast cancer, this epothilone B analogue, explained Dr. Huang, is a potent microtubule-stabilizing agent that is active in mRCC.

“It induces both tumor regression, retards tumor growth, and prolongs overall survival,” he stated.

The phase 2 trial included 87 patients with mRCC (65 men, 22 women; mean age, 56.1 years); 83% were Caucasian. Patients received ixabepilone 6 mg/m² per day intravenously for five days every two weeks. Most of these patients (76.7%) had clear-cell histology, most (91%) had undergone nephrectomy, and 51.7% had received no previous systemic or medical therapy. These patients had extensive disease at the time of enrollment, with a median total of 20.1 cm of measurable disease, as assessed in the RECIST trial (Response Evaluation Criteria in Solid Tumors), and a mean total tumor size larger than 24.3 cm. Most subjects had none (43%) or only one (43%) of the following risk factors: poor performance status, high corrected calcium, or anemia. Metastatic disease sites were most common in the lung (in 71 of 87 patients) and lymph nodes (in 68 of 87 patients). The trial’s primary endpoint was efficacy.

Patients received an average of 6.78 cycles (median, five cycles), with most patients (506 of 590) receiving a dose of 6 mg/m² per day; 14 patients received some cycles at lower doses, and 20 patients received some cycles at higher doses. Dr. Huang noted that tissue was obtained before and after treatment in the first cycle to evaluate target engagement.

The overall response rate was 12.6% (one complete response and 10 partial responses) with a median tumor shrinkage of 12% in the 37% of patients with measurable shrinkage. The median response duration was 5.5 months.

Tissue analysis showed microtubule stabilization in 84% to 92% of serial biopsies. Dr. Huang also mentioned that in the registration trial for sorafenib (Nexavar), overall survival was 19.3 months—15.9 months for placebo and 19.25 months for comparable patients receiving ixabepilone. He said that his team had developed an equation to estimate tumor regression and growth rates that correlated with overall survival. Applying this analysis to findings from this trial, compared with mRCC patients previously treated with placebo at the National Cancer Institute, the team noted that ixabepilone reduced the growth rate constant of mRCC by two-fold.

Dr. Huang concluded, “Ixabepilone is a potent microtubule-stabilizing agent active in metastatic renal cell cancer. It induces tumor regression and retards tumor growth while prolonging overall survival.”

Ixabepilone should be considered in combination with novel targeted therapies in future studies, he added.

Dasatinib (Sprycel) in Chronic Myelogenous Leukemia

Richard M. Stone, MD, Clinical Director, Adult Leukemia Program, Dana-Farber Cancer Institute, Boston, Mass.

Long-term follow-up of the Src/Abl Tyrosine Kinase Inhibition Activity Research Trial (START-C) of dasatinib 70 mg (Sprycel, Bristol-Myers Squibb) revealed continuing efficacy for the tyrosine kinase inhibitor (TKI) among patients with chronic-phase chronic myelogenous leukemia (CP–CML), according to Dr. Stone. The phase 2 START-C trial included 387 patients with CP–CML who received dasatinib 70 mg twice daily, all of whom were resistant to or intolerant of therapy with imatinib (Gleevec, Novartis). Eighty-two percent had a prior complete hematological response to imatinib, 37% had a major cytogenetic response (MCyR), and 19% had a complete cytogenetic response (CCyR) before imatinib failed. Ten percent of the patients had undergone stem cell transplantation.

Bcr–Abl mutations were present in 40%.

Reporting two-year results, Dr. Stone said that CCyRs were achieved by 53% of patients; among these patients, 79% had a major molecular response (MMR), defined as more than a 3-log reduction in Bcr–Abl burden. Overall, 62% had MCyRs, and 91% had complete hematological responses. Among those who entered the trial without a response at baseline (excluding imatinib-intolerant patients), rates were similar: complete hematological response, 87%; MCyR, 59%; and CCyR, 52%. The 91% progression-free survival rate at 12 months declined to 80% at 24 months, and the 97% overall survival rate at 12 months declined only slightly to 94% at 24 months.

Isolating the imatinib-resistant patients, whom Dr. Stone called “the worst of the worst,” he found that they did almost as well as patients who had prior responses. Their CCyR rate was 45% (among these, 70% had MMRs), and their MCyR rate was 55%. Progression-free survival (88% at 12 months) declined only to 75% at two years, and overall survival declined from 96% to only 92% over the same period.

“This is a drug that can deal with resistance,” Dr. Stone said.

The likelihood of response was similar regardless of mutation status, except for the T315I mutation. At 24 months, progression-free survival rates were 75% with any mutation and 83% without any mutations.

Concerns that longer-term treatment would exacerbate cytopenias were not borne out. Rates of leukopenia at 12 months
and at 24 months were the same (27%), and neutropenia rates (49% and 50%) and thrombocytopenia rates (48% and 49%) were similar. In addition, grade 3 and 4 nonhematological side effects did not increase substantially, and among patients who had been intolerant of imatinib, cross-intolerance to dasatinib was not observed.

“Dasatinib efficacy was demonstrated,” Dr. Stone concluded, “across subgroups, including all but one of 43 different baseline mutations.” He noted also that based on similar efficacy but a more favorable risk–benefit ratio, dasatinib 100 mg daily is the currently approved dose for patients with CP–CML.

Nilotinib (Tasigna) for Chronic Myelogenous Leukemia

Hagop M. Kantarjian, MD, MD Anderson Cancer Center, Houston, Tex.

Nilotinib (Tasigna, Novartis) had significant activity in chronic phase–chronic myelogenous leukemia (CML–CP), with a 91% survival rate at 18 months among 321 patients for whom imatinib therapy had failed, according to Dr. Kantarjian. The highly selective Bcr–Abl inhibitor, he said, binds to Abl with higher affinity and greater selectivity than imatinib mesylate (Gleevec) and inhibits most imatinib-resistant Bcr–Abl mutations (except the T315I mutation). Nilotinib was approved in the U.S. in October 2007 for patients with refractory CML–CP or those who did not tolerate previous therapy.

The primary endpoint of this clinical trial was the MCyR rate. Patients received nilotinib 400 mg orally twice daily two hours before or after meals. Their median age was 58 years, and the median duration of CML was 58 months. Prior imatinib therapy had ranged from 400 mg to more than 800 mg; 72% of patients had received 600 mg/day or more. The median duration of prior imatinib therapy was 33 months. The ratio of imatinib-resistant to imatinib-intolerant patients was 71% to 29%.

Patients received nilotinib at a median dose of 788 mg/day for a median of 465 days. Dose reductions were required in 25% of patients, and dose interruptions were needed for 55% for a median of 19 days.

The median time to achieve complete hematological response was one month, and the median time to achieve MCyRs was 2.8 months. Complete hematological responses were reported in 77% of the patients, with MCyR and CCyR rates at 58% and 42%, respectively. MCyRs were 56% for the imatinib-resistant patients and 63% for the imatinib-intolerant patients, and CCyRs were 39% and 50%, respectively. At 18 months, MCyRs were sustained in 84% of patients, and the progression-free survival rate was 67%; 95% of patients were alive at 12 months, and 91% were alive at 18 months. These durations exceeded those reported for other therapies and for allogeneic stem-cell transplantation.

Therapy was discontinued in 53% of patients (23% because of disease progression and 17% because of adverse events). Rash (in 30%), pruritus (in 25%), and nausea (in 24%) were the most common nonhematological adverse events, but grade 3 and 4 rates were 2% or lower. Biochemical abnormalities were noted in many patients, but grade 3 and 4 events were uncommon, consisting of lipase elevation (in 16%), hypophosphatemia (in 15%), hyperglycemia (in 12%), and total bilirubin, in 7%.

Rates for grade 3 and 4 anemia were 10%; for neutropenia, 30%; and for thrombocytopenia, 28%. The median duration of anemia was nine days, of neutropenia, 15 days; and of thrombocytopenia, 23 days. Grade 1 and 2 peripheral edema was reported in 6% of patients, and pericardial and pleural effusion were seen in 2% and 4% (all grades).

Results of this phase 2 trial, Dr. Kantarjian concluded, showed significant activity for nilotinib in CML–CP after unsuccessful imatinib therapy, with excellent tolerability and minimal occurrence of grade 3 and 4 adverse events.

Cetuximab (Erbitux) and Chemotherapy For Non–Small-Cell Lung Cancer

Robert Pirker, MD, Medical University of Vienna, Vienna, Austria

Thomas J. Lynch, Jr., MD, Harvard Medical School, Boston, Mass.

Results from the First-line in Lung cancer with Erbitux (FLEX) trial of cetuximab (Erbitux, Bristol-Myers Squibb/ImClone), added to first-line chemotherapy with cisplatin/vinorelbine (Platinol, Bristol-Myers Squibb)/Navelbine, GlaxoSmithKline), suggest the regimen as a new standard for the first-line treatment of advanced non–small-cell lung cancer (NSCLC). Dr. Pirker, lead investigator, noted that about 40% of NSCLC patients present with advanced disease and that epidermal growth factor receptor (EGF-R) expression is associated with tumor growth, metastasis, and a poor prognosis. Cetuximab is a monoclonal antibody that binds to EGF-R, blocking signal transduction and promoting receptor internalization (a process by which receptor signaling is down-regulated) and degradation.

The goal of FLEX was to demonstrate superior overall survival with cetuximab plus chemotherapy (arm A) versus chemotherapy alone (arm B). The investigators randomly assigned 1,125 patients with EGF-R–detectable advanced NSCLC, in a ratio of 1:1, to receive cetuximab 400 mg/m² as an initial dose, then 250 mg/m² per week plus cisplatin 80 mg/m² on day 1, as well as vinorelbine 25 mg/m² on days one and eight every three weeks (arm A). Patients in arm B received cisplatin/vinorelbine alone. The primary endpoint was overall survival.

Patients (median age, 59 years; 70% men) were naïve to both chemotherapy and anti–EGF-R therapy; 94% had stage IV NSCLC, 47% had adenocarcinoma, and 34% had squamous cell carcinoma. Eighty-three percent of the patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0/1. The median duration of treatment was 14 weeks.

Median overall survival was 11.3 months (a one-year survival rate of 47%) with chemotherapy/cetuximab and 10.1 months (one-year survival of 42%) with chemotherapy alone (HR = 0.871, P = 0.044). Dr. Pirker noted that the survival benefit was observed in the subgroups for ECOG status, smoking, histology, sex, age, and tumor stage. Median response rates were 36% with chemotherapy/cetuximab versus 29% for chemotherapy alone (P = 0.012); the median progression-free survival rate was 4.8 months in both groups. The time-to-treatment failure was 4.2 months for chemotherapy/cetuximab and 3.7
months for chemotherapy alone (HR = 0.860, P = 0.015).

Although median overall survival was longer for 121 Asians (19.5 months) than for 946 Caucasians (9.6 months) and for the chemotherapy-alone group than for the chemotherapy/cetuximab group, the small sample size in this trial did not allow for a definitive conclusion. The overall survival benefit for chemotherapy/cetuximab among Caucasians, when considered alone, was greater than in the overall group; median overall survival was 10.5 months vs. 9.1 months for chemotherapy alone (HR = 0.803, P = 0.003). The benefit was also noted for patients with adenocarcinoma, squamous cell carcinoma, and other histological diseases.

Side effects, Dr. Pirker said, were as expected and were manageable, with acne-like rash as the main cetuximab-related adverse event. He concluded that the cetuximab/chemotherapy regimen demonstrated better overall survival than chemotherapy alone in patients with advanced EGFR-R-expressing NSCLC.

He added, “Cetuximab added to a platinum-based chemotherapy sets a new standard for the first-line treatment of patients with advanced NSCLC.”

Dr. Lynch, an ASCO discussant, called the FLEX benefit “clinically meaningful,” but raised concerns about the 22% fever/neutropenia rate. He also commented that patient selection through biomarker analysis “may improve the cost effectiveness of this agent.”

IV Bisphosphonates versus Denosumab (AMG-162)

In Preventing Bone Turnover

- Julie Gralow, PharmD, University of Washington Cancer Care Alliance, Seattle, Wash.

Regardless of prior intravenous (IV) use of bisphosphonates, cancer patients with various tumor types who received denosumab, an investigational agent, had decreased markers of bone turnover, according to Dr. Gralow. She noted that although IV bisphosphonates are the current standard of care, “they have limitations in both efficacy and safety.”

Specifically, regarding safety, IV bisphosphonates are associated with renal toxicity; first-infusion effects, including fever, and chills; and osteonecrosis of the jaw (ONJ). Denosumab is a fully human monoclonal antibody that binds and neutralizes receptor activator for nuclear factor B ligand (RANKL). RANKL accelerates bone turnover and has been found to have harmful effects on bone volume and strength. Denosumab has demonstrated no renal toxicity, no first-infusion effects, and no ONJ to date, Dr. Gralow said.

Her study was designed to test whether earlier exposure to IV bisphosphonates affected denosumab’s ability to induce bone turnover suppression. Dr. Gralow compared results from studies of denosumab versus IV bisphosphonates in 255 bisphosphonates-naive patients (with breast cancer and bone metastases) and results in men or women (n = 111) with solid tumors and bone metastases or multiple myeloma, with high levels of bone resorption despite previous IV bisphosphonate therapy.

The key endpoints were three markers of bone turnover:

- serum C-telopeptide (sCTx)
- viable osteoclasts (tartrate-resistant acid phosphatase isoform 5b [TRAP 5b])
- bone-specific alkaline phosphatase (BSAP)

After 25 weeks of treatment, sCTx levels were reduced by about 80% with both IV bisphosphonates and denosumab in treatment-naive patients and by about 50% and 80%, respectively, with IV bisphosphonates and denosumab in patients with previous exposure to IV bisphosphonates.

TRAP 5b levels were reduced by 40% and by 60% in treat ment-naive patients who received IV bisphosphonates and denosumab and by about 10% and 70% with IV bisphosphonates and denosumab in patients who had previously been treated with IV bisphosphonates.

“The marked difference in TRAP 5b levels suggests the persistence of functioning osteoclasts despite treatment with IV bisphosphonates,” Dr. Gralow commented.

BSAP reductions were similar (40%) for both treatment groups and with both agents. Rates of adverse events were similar between the groups. For these two studies, Dr. Gralow concluded that denosumab’s inhibition of the RANKL pathway suppressed bone resorption regardless of patients’ previous exposure to IV bisphosphonates.

She said, “In patients still having active turnover despite being on IV bisphosphonates, being switched to denosumab gives a really dramatic and rapid decrease in markers of bone turnover. Ultimately, the combination of the two agents might prove to be more useful—hitting the osteoclasts in a couple of ways.”

Ipilimumab for Melanoma

- Steven O’Day, MD, Angeles Clinic and Research Institute, Santa Monica, CA
- Omid Hamid, MD, Angeles Clinic and Research Institute, Santa Monica, Calif.
- Jeffrey Weber, MD, PhD, Director, Donald A. Adam Comprehensive Melanoma Research Center, H. Lee Moffitt Cancer Center, Tampa, Fla.

Among nearly 500 patients with advanced melanoma who were treated with the investigational agent ipilimumab (MDX-010, Bristol-Myers Squibb) in pivotal trials, tumor growth was stopped within the first 12 weeks in about 30% of patients, followed by tumor shrinkage. After that, 10% to 20% of patients who had continued at first to progress then developed later responses, according to Dr. O’Day.

Ipilimumab is a fully human, monoclonal antibody directed against CTLA-4, a key negative regulator of T-cell response to tumor-associated antigens. Phase 3 trials of first-line ipilimumab with or without chemotherapy in melanoma are now under way.

The objective of Dr. O’Day’s open-label, multicenter study, which included 155 patients (median age 59 years, 52% male) with unresectable stage III or IV malignant melanoma, was to estimate the best overall response rate, as assessed by World Health Organization criteria. Patients received ipilimumab induction dosing of 10 mg/kg every three weeks for four cycles, with maintenance dosing every 12 weeks starting at week 24. Overall survival and survival at one year were

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secondary endpoints.

Reporting on the results, Dr. O’Day said that best overall response rate was 5.8% (for 9 of 155 patients), and the disease control rate (best response of complete plus partial responses plus stable disease) was 27.1% (in 42 of 155 patients). Despite the modest best overall response rate, median overall survival was 10.22 months and the one-year survival rate was 46.67%. These findings were “remarkably consistent” with those from two other ipilimumab trials in this population (by Dr. Hamid and Dr. Weber), which, together with Dr. O’Day’s study, included nearly 500 patients.

Dr. O’Day emphasized that best overall response did not accurately capture ipilimumab’s activity. Because with immunotherapy “you have to build up your army” (which takes 12 to 24 weeks), he said that survival is the more important endpoint and that early progression does not preclude a subsequent response. Also, even though survival time has typically been six to nine months with high-dose interleukin 2 (IL-2), with ipilimumab there is a plateau effect for about 30% of patients, with survival ranging from 10 to 15 months.

Grade 3 and 4 immune-related adverse events were reported in 21.9% of patients, with gastrointestinal effects the most common (8.4%). Long-term survival correlated highly with these immune overactivation side effects. Dr. O’Day commented further that IL-2 is given in hospitals or often in the intensive-care unit because of acute side effects—which do not correlate with better outcomes.

REFERENCE