Lapatinib Shows Promise in Early Trials

BY BRUCE JANCIN
Denver Bureau

San Antonio — The investigational drug lapatinib shows promise for the treatment of inflammatory breast cancer, the most aggressive form of primary breast cancer, Dr. Massimo Cristofanilli said at the annual breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Inflammatory breast cancer (IBC) accounts for just 1%-2% of all primary breast cancers. But it hasn’t received the research attention it deserves, given that it is notoriously difficult to treat and has a 5-year overall survival of only 40%, said Dr. Cristofanilli, codirector of the IBC clinic at M.D. Anderson Cancer Center, Houston.

The clinic, which opened last October, is the world’s first center dedicated to IBC research and treatment.

A retrospective analysis of nearly 400 patients with IBC who were treated using a multidisciplinary approach at M.D. Anderson during 1974-2005 underscores the long-standing lack of therapeutic progress, with no significant improvement seen in prognosis over the last 30 years.

Women with IBC haven’t benefited from the advances in locoregional and systemic therapies that have led to enormous improvements in outcome for non-inflammatory breast cancer, he said.

Up to 30% of women with IBC already have metastatic disease at the time of diagnosis of their primary breast cancer. Although IBC is a rapidly growing form of breast cancer, that’s only part of the reason for the high rate of metastases at initial diagnosis.

The fact is IBC is often diagnosed relatively late. Patients with IBC initially present with redness, swelling, tenderness, and pain that rapidly extends to the entire breast.

The breast skin has ridges and pits, like that of an orange, and the nipple is often inverted. Affected patients are often initially misdiagnosed as having mastitis and given antibiotics, the physician said.

Lapatinib (Tykerb) is an oral small-molecule tyrosine kinase inhibitor with activity against both the epidermal growth factor receptor (EGFR) and the HER2 receptor. Like trastuzumab (Herceptin), lapatinib appears to be effective in the treatment of HER2-positive breast cancers.

In addition, lapatinib has shown activity in patients with trastuzumab-resistant metastatic HER2-positive breast cancer. HER-2 overexpression has been reported in 30%-60% of cases of IBC.

Dr. Cristofanilli presented a phase II study involving neoadjuvant chemotherapy with lapatinib combined with paclitaxel in 35 patients newly diagnosed with IBC, including 9 who already had metastatic disease. A total of 30 patients had HER2 overexpressing tumors and the other 5 had HER2-negative disease that overexpressed EGFR.

Patients received 1,500 mg/day of lapatinib alone for 2 weeks, followed by 3 months of daily lapatinib plus once-weekly paclitaxel, then surgery.

The results exceeded anything previously seen in the treatment of IBC.

Among a total of 30 women with HER2-positive tumors, 23 patients showed a complete or partial clinical response, for an overall response rate of 77%.

Among the patients who have undergone definitive surgery, 3 of 18 women with HER2-positive and none of 3 patients with EGFR-positive disease.

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Three patients in the HER2-positive cohort had a complete clinical response while on lapatinib therapy.

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Women with early-stage breast cancer had significantly higher levels of 25 hydroxyvitamin D than women with advanced breast cancer.

Women with invasive breast cancer, including 204 with early-stage cancer and 75 with locally advanced or metastatic disease.

The investigators found significantly higher levels of 25 hydroxyvitamin D in the blood serum of women with early-stage breast cancer. The mean vitamin D level was 57 nmol/L in those women, compared with 46 nmol/L in the women with advanced breast cancer.

Parathyroid hormone levels also were significantly lower in the women with early-stage breast cancer: 3.91 pmol/L, compared with 5.06 pmol/L in the women with advanced or metastatic breast cancer.

The researchers, led by Dr. Carlo Palmieri of Imperial College in London, wrote that the study does not determine whether the reduced vitamin D levels helped contribute to advanced cancer or whether it is a consequence of “reduced dietary intake or altered synthesis in the skin due to reduced sun exposure” in those patients with more advanced disease.

In summary, these findings lend support to the hypothesis that vitamin D has a role in the pathogenesis and progression of breast cancer, the authors said (J. Clin. Pathol. 2006 Oct 17 [Epub doi: 10.1136/jcp.2006.042747]).

Animal studies have shown that vitamin D can inhibit growth of breast cancer cell lines and development of carcinogen-induced mammary tumors as well as by promotion of apoptosis, although the exact mechanisms are not clear, they noted.

Monitor Vitamin D With Bisphosphonate Use

BY BRUCE JANCIN
Denver Bureau

San Antonio — Vitamin D deficiency is surprisingly common in breast cancer patients who are on bisphosphonates for treatment of bone metastases or osteoporosis due to hormone ablation therapy. Dr. Andrea Wang-Gillam reported at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Of a series of 212 breast cancer patients taking a bisphosphonate, 61% had vitamin D inadequacy as defined by a serum 25-hydroxyvitamin D (25[OH]D) level of 30 ng/mL or less.

That’s a disturbingly high rate, she noted, particularly in light of emerging reports that bisphosphonate therapy in patients with occult vitamin D deficiency can have serious adverse consequences, including secondary hyperparathyroidism and prolonged symptomatic hypocalcemia.

Moreover, vitamin D deficiency can render the bisphosphonate therapy ineffective, according to Dr. Wang-Gillam of the University of Arkansas, Little Rock.

In this series of breast cancer patients on bisphosphonates, 34% had a serum 25(OH)D level of 20-30 ng/mL and 20% had a level of 10-19 ng/mL.

Secondary hyperparathyroidism as defined by a parathyroid hormone level in excess of 65 pg/mL in the presence of a low or normal serum calcium level was present in 15% of women with a serum 25(OH)D level of 20-30 ng/mL and in a higher proportion of patients with more extreme vitamin D deficiency.

Among the subset of 57 women on highly potent intravenous bisphosphonates, only 24 had a serum 25(OH)D measurement recorded in their chart; 15 of these had vitamin D inadequacy.

Dr. Wang-Gillam recommended that physicians routinely measure serum 25(OH)D, calcium, and parathyroid hormone levels in breast cancer patients for whom bisphosphonate therapy is being considered so that adequate vitamin D supplementation can be introduced prior to starting the drug.

She cautioned, however, that profound vitamin D deficiency can occur despite vitamin D supplementation.

For example, of the 15 patients in the series who had a 25(OH)D level below 10 ng/mL, 3 had a total daily vitamin D intake of at least 600 IU and 2 others were getting less than 600 IU daily.

Vitamin D Varies With Ca Severity

BY JONATHAN GARDNER
London Bureau

Women with early-stage breast cancer have higher levels of vitamin D and lower levels of parathyroid hormone in their bloodstream than women with advanced or metastatic breast cancer, according to an observational study published in the Journal of Clinical Pathology.

Past epidemiologic studies have suggested a link between higher vitamin D levels through exposure to sunlight and reduced prevalence of breast cancer. Previous research also has demonstrated that vitamin D levels are higher in healthy women when compared with those with primary breast cancer, and levels decrease with progression of bone metastases.

In the current study, researchers prospectively evaluated 279 white women with early-stage breast cancer who had undergone definitive surgery, 3 of 18 women with HER2-positive and none of 3 patients with EGFR-positive disease.

Among the patients who have undergone definitive surgery, 3 of 18 women with HER2-positive and none of 3 patients with EGFR-positive disease.

The phase II trial was sponsored by GlaxoSmithKline.