Chemotherapy Foundation Symposium XXVI Roundup

Key findings on breast, lung, ovarian, and other cancers — Diane West

The Chemotherapy Foundation, created in 1968, began hosting the Chemotherapy Foundation Symposium in 1972. The Symposium was initially held biannually and is now an annual event. The Foundation’s goal in hosting the Symposium is to provide an avenue for researchers to apprise community oncologists on the latest developments in cancer diagnosis and treatment.

This year’s conference took place in New York City on November 4-8. Writers for Oncology & Biotech News attended so that we might bring you key highlights on gynecologic, breast, lung, prostate, and hematologic cancer research presented at this important meeting. While some of the findings had been presented at other conferences and discussed in prior issues of Oncology & Biotech News, they have been included because they constitute some of the primary studies presented at the Symposium.

**Breast Cancer**

Trastuzumab/Lapatinib Doublet Bests Lapatinib Monotherapy

Earlier randomized studies led by Harold Burstein, MD, PhD, assistant professor of medicine at Harvard Medical School and a medical oncologist in the HER2-positive breast cancer, combination therapy maintained better quality of life (as compared to baseline measures) than women in the monotherapy group. The trial also affirmed the results of earlier studies showing improved PFS for patients in the combination group. Dr. Burstein said that 2 large trials—CALGB 40601 and ALTTO—are now accruing to test the trastuzumab/lapatinib combination “in a more rigorous fashion.”

Antibody Conjugate May Pack Targeted Punch for Trastuzumab

Although trastuzumab (Herceptin) has revolutionized breast cancer treatment, concerns persist about resistance (initial and eventual) and toxicity. Trastuzumab-DM1, a first-in-class antibody drug conjugate for HER2-positive breast cancer, combines trastuzumab’s HER2-blocking activity with the targeted delivery mechanism of DM1 and is being studied as a possible solution to these concerns.

Phase II studies commenced last summer to evaluate the effects of trastuzumab-DM1 in patients with trastuzumab-resistant HER2-positive metastatic breast cancer. If the outcomes are favorable, Ian E. Krop, MD, MA, chief of breast medical oncology at Dana-Farber Cancer Institute, Boston, Massachusetts, found that breast cancer patients receiving trastuzumab (Herceptin) plus lapatinib (Tykerb) had a longer period of PFS than patients on lapatinib monotherapy (P = .008). The previous trials also documented significantly improved rates of complete response, partial response, and stable disease for women in the combination arm.

Dr. Burstein followed up these trials with a similar randomized study that assessed quality of life for patients receiving the combined trastuzumab/lapatinib regimen, which he described as an “upstairs/downstairs” approach to treating HER2-positive breast cancer, versus those on lapatinib alone. Investigators enrolled 296 women who had HER2-positive metastatic breast cancer, some who had undergone multiple rounds of chemotherapy, and randomized them 1:1 to either cohort. The study concluded that women receiving combination therapy maintained better quality of life (as compared to baseline measures) than women in the monotherapy group. The trial also affirmed the results of earlier studies showing improved PFS for patients in the combination group. Dr. Burstein said that 2 large trials—CALGB 40601 and ALTTO—are now accruing to test the trastuzumab/lapatinib combination “in a more rigorous fashion.”
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(Continued from cover)

of the Dana-Farber Cancer Institute said “it would confirm HER2 remains a valid target even after multiple lines of HER2-directed therapy.” He added that such a finding would be encouraging for trastuzumab-resistant patients because of the “huge number of new HER2-targeted agents in the pipeline.”

Tamoxifen Not Always the Best Choice

Tamoxifen (Nolvadex) may not be a ‘one-size-fits-all’ drug, as some oncologists have long regarded it, according to Samuel Waxman, MD, founder and scientific director of the Samuel Waxman Cancer Research Foundation. Dr. Waxman said this is particularly true in patients with ER-positive breast cancer who overexpress cyclin D1. He suggested that fulvestrant (Faslodex) may be a better choice for such patients, but not necessarily as a single agent. Dr. Waxman and colleagues have proposed combining fulvestrant with the proteasome inhibitor bortezomib (Velcade), a hybrid approach they dub “proteocine therapy.” Investigators are developing a phase II study to investigate the drug combination in postmenopausal, ER-positive women with a diagnosis of recurrent local and metastatic breast cancer.

Immunotherapy: Breast Cancer’s Next Frontier?

Using immunotherapy to treat cancer—including breast cancers—continues to garner interest. Thus far, only the results of small phase I studies are available, but one agent is generating optimism: lapuleucel-T (Neuvenge). This investigational product is one of a new class of active cellular immunotherapies created by exposing a patient’s cells, exposing the cells to lapuleucel, and then reinfusing them. A cumulative 37 patients with advanced or metastatic breast, ovarian, or colorectal cancer have undergone the procedure in 2 phase I trials. According to John Park, MD, University of California San Francisco Helen Diller Family Comprehensive Cancer Center, some patients showed a “robust immune response.” Stable disease lasting >1 year was achieved in 5 patients, and 1 patient achieved a partial response. Dr. Park noted that positive responses unfortunately declined over time, but said that the early results suggest the treatment “warrant[s] further study.”

Chemotherapy Foundation Symposium XXVI Highlight

Lenalidomide for Blood Cancers: Alone or in Combination

The advent of lenalidomide (Revlimid), a type of angiogenesis inhibitor similar to thalidomide, and the possibility of combining lenalidomide with older drugs or combining older drugs in new ways may offer options for patients with hematological cancer, such as multiple myeloma (MM). In the United States, about 8 phase III trials are underway.

Researchers are investigating new configurations for traditional therapies or combining them with newer agents like lenalidomide for use in patients with MM. David H. Vesole, MD, PhD, FACP, a hematologist expert for the Multiple Myeloma Program at St. Vincent’s Comprehensive Cancer Center in New York City, said that these trials have cumulative response rates of ~40% to 50% and overall response rates in the 80% range. “Almost all show about a 2-year time to progression,” he said. “But what’s even more impressive,” he added, “is that 1-year survivals exceed 90% in virtually all the studies.” Dr. Vesole noted that toxicity is a drawback and cautioned that different treatments have different toxicities. “The thalidomide-based regimens are obviously associated with increased deep venous thrombosis, bortezomib increases the risk of peripheral nervous system diseases, and it’s a tussup as to which [regimen] causes more cytopenias.” Whether the patient is or could become eligible for a transplant might also affect the clinician’s choice of treatment for patients with MM.

Dr. Vesole identified several “main” US trials for patients with MM: melphalan hydrochloride (Alkeran); prednisone and thalidomide (MPT) versus melphalan; prednisone and lenalidomide; bortezomib (Velcade) versus dexamethasone (Decadron) versus a combination of the two; and standard dexamethasone versus high-dose dexamethasone versus a combination of the two (this trial is still accruing).

Lenalidomide may also play an increasingly important role in the treatment of chronic lymphocytic leukemia (CLL) because of its ability to target tumors at the microenvironment level, according to Asher A. Chanan-Kahn, MD, associate professor of oncology, Roswell Park Cancer Institute, and assistant professor of medicine, State University of New York at Buffalo. Dr. Chanan-Kahn said that at least 2 small and mid-sized studies in 2008 found that combination therapy regimens including lenalidomide demonstrated anti-leukemic effects in patients with relapsed and refractory CLL. There is also evidence that lenalidomide may be effective as a single agent in the first-line setting. “Our limited experience demonstrates so far that lenalidomide in combination with rituximab is not only feasible, but is able to deliver clinical responses even in patients who had [previously become resistant to] lenalidomide,” said Dr. Chanan-Kahn. If results from the small studies are encouraging, researchers will move forward.
Sunitinib Takes Aim at Non–small Cell Lung Cancer

The tyrosine kinase inhibitor sunitinib (Sutent), used to treat some aggressive gastric cancers and advanced kidney cancer, is being investigated as a possible treatment for patients with non–small cell lung cancer (NSCLC). Study chair Mark A. Socinski, MD, University North Carolina Lineberger Comprehensive Cancer Center, said that treating patients who have NSCLC with sunitinib presents “more issues than answers” in terms of proper dosing and whether it is effective when combined with other agents.

To examine these issues more closely, Socinski and colleagues are currently accruing patients to 2 randomized double-blind trials. CALGB 30607 will study sunitinib versus placebo as maintenance therapy in 156 patients with advanced (stage IIIB/IV) stable or responding NSCLC who were treated previously with 4 cycles of standard platinum-based therapy. Patients who received chemotherapy with bevacizumab (Avastin) are eligible for the phase III study provided they have not received bevacizumab beyond the 4 chemotherapy cycles. End points of the study include tumor response and quality of life. Investigators will conduct a correlative science study “to help determine which patients are more likely to benefit from drugs like sunitinib.”

The other trial, CALGB 30704, is a multicenter study. Investigators plan to enroll 225 patients with advanced NSCLC that has continued to progress subsequent to first-line treatment (which cannot include more than 1 regimen of chemotherapy). Patients will be randomized to receive sunitinib, the enzyme inhibitor pemetrexed (Alimta), or sunitinib plus pemetrexed; the 18-week rate of PFS serves as the primary outcome measure. Researchers hope to document early predictors of likely response to these second-line treatments.

Antibiotic Amrubcin Studied in Small Cell Lung Cancer

Anthracyclines are commonly used to treat various carcinomas, including lung cancer, but they are associated with significant cardiotoxicity in some patients. Researchers are hoping that the experimental chemotherapy drug amrubcin may provide an alternative for these patients. Amrubcin is a third-generation synthetic anthracycline and potent topoisomerase II inhibitor, described by Robert M. Jotte, MD, PhD, Rocky Mountain Cancer Centers, Denver, Colorado, as being “similar to doxorubicin [but] devoid of typical anthracycline cardiac toxicity.” Amrubcin is already approved in Japan as a treatment for lung cancer. In a trial comparing amrubcin with topotecan hydrochloride (Hyca- mitin) in patients with extensive disease small cell lung cancer (SCLC), patients receiving amrubcin demonstrated an overall tumor response rate of 36% versus 8% for the topotecan cohort. The rate of PFS was about the same in both arms, and after 1 year, there was no significant difference in the rate of overall survival between the 2 groups. Most notably, researchers noted no cardiomyopathy in study patients treated with amrubcin.

Investigators are now accruing 480 patients with extensive or limited SCLC who have progressed following first-line treatment to a phase III trial. This trial will compare overall survival of amrubcin versus topotecan as a second-line treatment for patients with SCLC.

Immunotherapy and Vaccines in Lung Cancer

Just as with other cancers, immunotherapy and vaccines are being investigated for their possible applicability to lung cancer. Talactoferrin alfa (TLF), an oral fungus-derived medication, works in the gut and may stimulate the immune system. According to Giuseppe Giaccone, MD, chief of the medical oncology branch at the NCI in Bethesda, Maryland, 2 concurrent phase III trials investigating TLF are being planned. One will investigate TLF as a first-line treatment for patients with non–small cell lung cancer (NSCLC) in combination with carboplatin/paclitaxel (Taxol) chemotherapy versus chemotherapy alone. The other trial will measure response rates in 720 patients with recurrent advanced (stage IIIB/IV) NSCLC who have failed ≥2 previous therapies. Patients will receive standard supportive care and be randomized to receive single-agent treatment with TLF or placebo, with overall survival as a primary end point.

MAGRIT (MAGE-A3 as Adjuvant NSCLC Immunotherapy) is another large phase III trial currently accruing. Researchers are seeking to determine whether overexpression of melanoma antigen family A3 (MAGEA3) predicts response to a new experimental vaccine, explained Nasser Altorki, MD, professor of cardiothoracic surgery and director of the Division of Thoracic Surgery at New York Presbyterian-Weill Cornell Medical Center.

The phase III START (Stimulating Targeted Antigenic Responses to NSCLC) trial is also enrolling patients. START is a multicenter randomized double-blind placebo-controlled study of the cancer vaccine BLP-25 (Stimuvax) in patients with unresectable stage III NSCLC.

Molecular Markers in Non–small Cell Lung Cancer

The mitotic inhibitor docetaxel (Taxotere) gave patients with recurrent non–small cell lung cancer (NSCLC) a second-line option in the late 1990s. It was followed by pemetrexed (Alimta), which some researchers say is less toxic than docetaxel. The tyrosine kinase inhibitor (TKI) erlotinib (Tarceva) is now routinely used as second and third-line therapy for incurable NSCLC.

Clinicians generally agree that drugs known to inhibit EGFRs, such as TKIs, are a good choice for patients with recurrent NSCLC. Yet, Fred Hirsch, MD, PhD, professor of medicine, University of Colorado Cancer Center, Aurora, notes that ~50% of patients will respond, while ~30% will derive no benefit and die within 2 to 3 months. Dr. Hirsch believes that “EGFR-FISH is a good predictive marker for EGFR-TKI therapy,” and he explained that some preliminary studies suggest patients with higher EGFR gene copy numbers respond better to TKIs. He added that other markers, such as KRAS mutations, may also be found to predict whether NSCLC patients will show positive tumor response to particular therapies.

Corey J. Langer, MD, director of thoracic oncology at University of Pennsylvania’s Abramson Cancer Center in Philadelphia, predicted that successful isolation of certain molecular markers may usher in another wave of options for these patients. In October 2008, the NCI launched the phase II MARVEL (Marker Validation for Erlotinib in Lung Cancer) study, which it describes as the “first-ever study to determine if biomarkers can help guide treatment for lung cancer.” This collabora-
Trabectedin Shows Promise in Recurrent Ovarian Cancer

Trabectedin (Yondelis), a tetrahydroisoquinoline alkaloid derived from a Caribbean sea squirt, is believed to interfere with DNA repair in cancer cells and may offer a new option for patients with recurrent ovarian cancer. Trabectedin is already approved in Europe and has orphan drug status in the United States. Investigators said that “pro-vocative activity” in phase I and II trials combining trabectedin and doxorubicin HCl liposome injection (Doxil) in chemo-sensitive patients with recurrent ovarian cancer encouraged the launch of a global multicenter phase III trial.

All women had progressed after 6 full cycles of chemotherapy; two-thirds experienced relapse ≤ 6 months after the last dose of first-line therapy. One arm (n = 335) received pegylated liposomal doxorubicin (PLD) at the FDA-approved dosage of 50 mg/m² in 90-minute infusions every 4 weeks. The other (n = 337) received combination therapy with PLD 30 mg/m² over 60 to 90 minutes followed by a 1.1 mg/m², 3-hour infusion of trabectedin every 3 weeks. “Importantly, this was a mixed population,” noted Bradley J. Monk, MD, Comprehensive Cancer Center, University of California, Irvine, referring to variation in types of ovarian cancer among the patients.

Dr. Monk said that in platinum-sensitive patients with recurrent disease “both the investigators and an independent reviewer found a 47% response rate in patients with the nonplatinum combination therapy,” which he described as competitive to platinum-based therapies, although he added that “direct comparisons cannot be made.” PFS was ~2 months longer in the combination therapy arm compared with the PLD single-therapy group (7.3 m vs 5.8 m, respectively; HR, 0.79; P = .019).

No detriment was observed when trabectedin was added to PLD, but Dr. Monk emphasized that the survival data “are not yet mature.” Patients were checked weekly for transaminitis, an adverse effect associated with trabectedin that can indicate liver problems. Dr. Monk concluded that the “data demonstrate a role for a nonplatinum doublet in this population,” and disagreed with any suggestion that a 1.5-month increase in PFS was minimal. “In the world of ovarian cancer,” he said, “this difference is huge.” (For additional information on this study, please see our previous coverage in Oncology & Biotech News, Nov/Dec issue, page 29).

Kick-Starting Response in Platinum-Resistant Ovarian Cancer

When women with ovarian cancer demonstrate resistance to platinum-based drugs like oxaliplatin (Eloxatin), oncologists often try switching them to another platinum-based chemotherapy, hoping to kick-start tumor response. Britta K. Stordal, MD, postdoctoral scientist, Bill Walsh Cancer Research Laboratories, Royal North Shore Hospital, University Of Sydney, St. Leonards, Australia, questions this approach.

“Oxaliplatin should not be used in the treatment of cisplatin (Platinol)-resistant cancer purely based on its resistance profile alone,” she said. Instead, she suggests alternating between platinum-based therapies and taxanes, like paclitaxel (Taxol) and docetaxel (Taxotere). “Very few cell lines are resistant to both pacli-taxel and cisplatin,” Dr. Stordal said, “so alternating between the two may have some clinical benefit.”

Intraperitoneal Versus Intravenous Chemotherapy

Franco M. Muggia, MD, New York University School of Medicine, addressed the ongoing debate initiated by the NCI’s 2006 assertion that women with ovarian cancer who have undergone surgery experience longer overall survival with combination intraperitoneal (IP) chemotherapy than with intravenous (IV) chemotherapy. Dr. Muggia said he and several of his colleagues question this conclusion. He noted that IP delivery of a drug like paclitaxel (Taxol) can be highly toxic and cause adverse effects severe enough to stop therapy.

Dr. Muggia added that he believes the majority view chemotherapy with IV carboplatin and paclitaxel as the “gold standard” for women with ovarian cancer, unless a “feasible regimen would confirm a superior efficacy in a properly designed clinical trial with an adequate control arm.” He said, “The role of paclitaxel is uncertain, but its toxicity is unquestionable, so leave it out of the IP regimen.” He noted that chemotherapy including IP cisplatin (Platinol) is largely unexplored and may yield improved results. He concluded that pilot studies have yielded preliminary results that suggest further testing of this regimen may be warranted.

Receptors May Signal Prostate Cancer Treatment

In the United States, prostate cancer is the second most common type of cancer in men, with about 186,320 new cases diagnosed each year. The disease can be detected early with routine screening and has a low risk of death if caught promptly. Men with prostate cancer have several treatment options, including hormones. Prognosis is less favorable in men who have hormone-resistant prostate cancer (HRPC) and men with bone metastases. These hard-to-treat cases can be identified using endothelial-A (EIA) receptor signaling.

Recent phase II trials of a new ETA receptor antagonist, ZD4054, found that the drug showed promise in patients with HRPC and bone metastases. Overall survival for patients was 24 months versus 17 months for those receiving placebo. Nancy A. Dawson, MD, director of the Genitourinary Oncology Program, Lombardi Comprehensive Cancer Center, and professor of medicine and oncology at Georgetown University, Washington, DC, said the agent is now in phase III trials.

New options may also be on the horizon for men with castrate-resistant prostate cancer, especially if the tumor—not the gonads—is expressing androgens. In a small subset of these patients, inhibition of the enzyme CYP17A1 with abiraterone acetate (CB7630) produced a dramatic response after 6 months to 1 year of therapy, noted Elena Efstathiou, MD, PhD, instructor, Department of Genitourinary Oncology at M. D. Anderson Cancer Center. Researchers are focusing on identifying possible predictors of early disease progression, including depleted testosterone levels at the microenvironment.

Dr. Stordal pooled data from several studies to support this theory. One study examined paclitaxel treatment in ~2000 women with ovarian cancer who had developed resistance to cisplatin and had never received paclitaxel previously. Overall, 8% of patients who switched to oxaliplatin showed tumor response; 22% responded to paclitaxel. Patients in a group that was given a combination of cisplatin and paclitaxel as a first-line treatment (n = 232) did even better when they received paclitaxel in the second-line setting, demonstrating a response rate of 35%. “Let’s just think about this for a moment,” Dr. Stordal suggested. “We’re actually seeing a higher response rate in patients who’ve already been treated with paclitaxel.” She noted that this is the reverse of what would normally be expected with chemotherapy treatment.