HEM/ONC News

By Stacey Small

Long-Term Overall Survival Improved With the Addition of Trastuzumab to Chemotherapy in Patients With HER2-Positive Breast Cancer

In the combined National Surgical Adjuvant Breast and Bowel Project B-31 study and the North Central Cancer Treatment Group N9831 trials, patients with operable human epidermal growth factor receptor 2 (HER2)-positive breast cancer received chemotherapy consisting of doxorubicin plus cyclophosphamide followed by paclitaxel. They were randomly assigned to receive either trastuzumab for 1 year or no trastuzumab. At a median of 8.4 years, 84% of patients in the trastuzumab cohort were alive versus 75.2% of patients who were treated with similar chemotherapy but did not receive trastuzumab ($P<.0001$). At every 2-year time point, the difference in survival widened between the groups. The absolute difference in overall survival was 2.9% at 4 years, 5.5% at 6 years, 7.6% at 8 years, and 8.8% at 10 years. Chemotherapy plus trastuzumab reduced the risk of a disease-free survival event at 10 years by 40% ($P<.0001$). There were 680 events among the 2,018 patients who received chemotherapy alone compared with 473 events among the 2,028 patients who received additional trastuzumab. Thirty-one patients in the chemotherapy-only group and 38 patients in the trastuzumab group died without recurrence. Data were presented by Romond and associates at the 35th Annual San Antonio Breast Cancer Symposium (SABCS; Abstract S5-5).

Durable Survival Benefit Achieved With the Addition of Everolimus to Exemestane in Advanced Breast Cancer

According to results presented by Piccart and colleagues at the 35th Annual SABCS (Abstract P6-04-02), the addition of everolimus (Afinitor, Novartis) to exemestane offered superior long-term survival over exemestane alone in postmenopausal patients with hormone receptor-positive advanced breast cancer that had progressed after nonsteroidal aromatase inhibitor therapy. Data were from the final progression-free survival (PFS) analysis of patients who were enrolled in the Breast Cancer Trials of Oral Everolimus (BOLERO)-2 study. Per local assessment, the addition of everolimus to exemestane significantly extended median PFS versus exemestane monotherapy (7.8 months vs 3.2 months; hazard ratio [HR]=0.45; $P<.0001$). Similar results were obtained on central assessment (median of 11 months vs 4.1 months for the 2 treatments, respectively [HR=0.38; $P<.0001$]). There were fewer deaths in the exemestane plus everolimus arm than in the exemestane-alone arm. Overall survival events occurred in 25.4% and 32.2% of the 2 arms, respectively. There was a more than 4-month improvement in PFS in the exemestane plus everolimus arm, irrespective of the presence of visceral or bone metastases. Patients with visceral metastases had a 53% risk reduction for PFS, and patients without visceral metastases had a 59% risk reduction for PFS. Most adverse events were low grade and manageable. Pneumonitis and interstitial lung disease occurred only in the exemestane plus everolimus arm.

Eribulin Mesylate Is Not Superior to Capecitabine in Previously Treated Patients With Metastatic Breast Cancer

According to results of a phase III trial presented by Kaufman and coworkers at the 35th Annual SABCS (Abstract S6-6), eribulin mesylate (Halaven, Eisai Inc.) did not show a statistically significant survival benefit compared with capecitabine (Xeloda, Roche) in patients with previously treated metastatic breast cancer. However, this was the first study to demonstrate activity of eribulin in the first-, second-, and third-line setting in metastatic breast cancer. The study randomized 1,102 patients to receive either eribulin mesylate 1.4 mg/m^2 administered on days 1 and 8 of a 21-day cycle or capecitabine 1,250 mg/m^2 administered orally twice daily on days 1–14 of a 21-day cycle. Patients had locally advanced or metastatic breast cancer, no more than 3 prior chemotherapy regimens (≤2 for advanced disease), and prior treatment with anthracycline and taxane chemotherapy. Baseline characteristics were well balanced between the 2 treatment arms. The median overall survival was 15.9 months for eribulin and 14.5 months for capecitabine (HR=0.879; 95% confidence interval [CI], 0.770–1.003; $P=.056$). Median PFS was 4.1 months and 4.2 months, respectively (HR=1.079; 95%

CI, 0.932–1.250; *P*=.305). Overall response rates were 11% for eribulin and 12% for capecitabine (*P*=.849). The overall survival was 15.9 months for patients treated with eribulin and 13.5 months for patients treated with capecitabine (HR=0.838; 95% CI, 0.715–0.983; *P*=.030). A prespecified subgroup analysis determined that particular patient subgroups may achieve greater therapeutic benefit from eribulin, including patients whose breast cancer is triple-negative (HR, 0.702), estrogen-receptor negative (HR, 0.779), and HER2-negative (HR, 0.838). Adverse events occurring in more than 20% of patients included neutropenia (54% for eribulin vs 16% for capecitabine), hand-foot syndrome (<1% vs 45%, respectively), alopecia (35% vs 4%, respectively), leukopenia (31% vs 10%, respectively), diarrhea (14% vs 29%, respectively), and nausea (22% vs 24%, respectively).

Concurrent Brentuximab Vedotin With Multi-Agent Chemotherapy For the Frontline Treatment of ALCL and Other CD30-Positive Mature T-Cell and NK-Cell Lymphomas

At the 54th Annual Meeting of the American Society of Hematology (ASH), Fanale and associates reported on a phase I, open-label, multicenter trial that enrolled 39 patients with higher-risk systemic anaplastic large cell lymphoma (sALCL) or other CD30-positive mature T-cell and natural killer (NK)-cell lymphomas (Abstract 60). The primary goal of the study was to determine the safety of combination brentuximab vedotin (Adcetris, Seattle Genetics) plus cyclophosphamide, doxorubicin, and prednisone (CHP) for the frontline treatment of CD30-positive T-cell and NK-cell lymphomas, including sALCL. In addition, the investigators sought to determine the recommended dose of brentuximab vedotin when used as a combination therapy with CHP. Patients were randomized to receive 2 cycles of brentuximab vedotin 1.8 mg/kg every 3 weeks followed by 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or 6 cycles of brentuximab vedotin 1.8 mg/kg plus standard-dose CHP every 3 weeks. Patients who responded to therapy were treated with single-agent brentuximab vedotin every 3 weeks for an additional 10 cycles. Data from brentuximab vedotin plus CHP were presented. Of the 26 patients treated with brentuximab vedotin and CHP (15 female; median age, 55.5 years), 19 patients had sALCL, 2 patients had peripheral T-cell lymphoma, 2 patients had angioimmunoblastic T-cell lymphoma, 2 patients had adult T-cell leukemia/lymphoma, and 1 patient had enteropathy-associated T-cell lymphoma. The maximum tolerated dose of brentuximab vedotin plus CHP was not exceeded, as evidenced by the 1 grade 3 rash reported in 6 patients. Treatment-emergent adverse events that occurred in more than 30% of patients included nausea (62%), peripheral sensory neuropathy (62%), diarrhea (58%), fatigue (54%), alopecia (46%), dyspnea (38%), constipation (35%), cough (35%), and febrile neutropenia (31%). Among the 18 patients (69%) who developed peripheral neuropathy, 16 had peripheral sensory neuropathy, 3 had muscular weakness, 2 had peripheral motorneuropathy, 1 had burning sensation, 1 had paresthesia (grade 3), 1 had peripheral sensorimotor neuropathy, and 1 patient had peroneal nerve palsy. Peripheral neuropathy was managed with dose delays in 4 patients and dose reductions in 7 patients. The most common grade 3 or higher adverse events included febrile neutropenia (19%), nausea (8%), neutropenia (8%), and pulmonary embolism (8%). Treatment discontinuation due to adverse events occurred in 6 patients (23%). There were no infusion-related reactions. Clinical response was assessed in 23 patients at the end of 6 cycles of brentuximab vedotin plus CHP and in 3 patients who discontinued treatment before cycle 6. Of the 26 patients, 21 received single-agent brentuximab vedotin after combination therapy. Eight patients remain in treatment. An objective response was achieved in 100% of patients. Complete remission was achieved in 23 patients (88%), which included 16 patients with sALCL and 7 patients with other CD30-positive lymphomas. Two patients experienced disease progression. The median PFS and overall survival have not yet been reached. The investigators concluded that frontline treatment of sALCL and other CD30-positive T-cell and NK-cell lymphomas with brentuximab vedotin 1.8 mg/kg plus CHP every 3 weeks had a manageable safety profile and promising clinical efficacy. A phase III study of brentuximab vedotin plus CHP versus CHOP alone for the frontline treatment of mature T-cell lymphomas is scheduled to begin this year.