HEM/ONC News

By Stacey Small

Long-Term Data Suggest Chemotherapy Alone Is Superior to Radiation-Based Therapy in Patients With Limited-Stage Hodgkin Lymphoma

According to research published in the December 11 online issue of the *New England Journal of Medicine*, treatment with ABVD chemotherapy (doxorubicin [Adriamycin], bleomycin [Blenoxane], vinblastine [Velbe], and dacarbazine) alone is associated with lower 12-year mortality compared to the use of a radiotherapy-based treatment in patients with limited-stage Hodgkin lymphoma, mainly due to fewer deaths from other causes. Meyer and associates initiated the HD.6 (Hodgkin's Disease.6) study in 1994 in order to compare chemotherapy alone to radiotherapy-based treatment in patients with low-risk stage IA or IIA non-bulky Hodgkin lymphoma. Previously reported results from a median follow-up of 4.2 years revealed no difference in overall survival between the treatment groups. The results of the final analysis of the study were presented in December 2011 at the annual meeting of the American Society of Hematology. A total of 405 patients with stage IA or IIA non-bulky Hodgkin lymphoma were randomized to receive first-line treatment with ABVD alone (4–6 cycles), or subtotal nodal radiation therapy with or without ABVD. (Patients with an unfavorable risk profile received ABVD, whereas those with a favorable risk profile did not receive ABVD.) The primary endpoint was 12-year overall survival. After a median follow-up of 11.3 years, the 12-year overall survival rate for patients receiving ABVD alone was 94% versus 87% for patients receiving subtotal nodal radiation therapy (hazard ratio [HR] for death with ABVD alone, 0.50; 95% confidence interval [CI], 0.25–0.99; *P*=.04). The rates of freedom from disease progression were 87% among patients treated with ABVD alone versus 92% among patients receiving subtotal nodal radiation therapy (HR for disease progression, 1.91; 95% CI, 0.99–3.69; *P*=.05). The rates of event-free survival were 85% and 80%, respectively (HR for event, 0.88; 95% CI, 0.54–1.43; *P*=.60). In the ABVD-alone treatment arm, there were 6 patients who died from Hodgkin lymphoma or an early treatment complication, and 6 deaths from another cause. Among patients who received radiation-based treatment, 4 deaths were related to Hodgkin lymphoma or early toxic effects from the treatment, and 20 deaths were related to another cause. The investigators noted that a major limitation was the now-outdated subtotal nodal radiotherapy used in this study, and that the extent of radiotherapy is very likely to have contributed to the excess mortality observed. They also acknowledge the need for longer-term follow-up of survival, and are certain that therapeutic advances will occur in the interim. Improving long-term survival in patients with low-risk stage IA or IIA non-bulky Hodgkin lymphoma may be less dependent on reducing deaths due to progressive disease than previously thought, with more emphasis needed on reducing late treatment effects; trial endpoints should therefore capture such data. The authors conclude that ABVD alone in this setting can now more confidently be considered a therapeutic option for this patient population.

Aflibercept Shows Clinical Activity for Malignant Ascites in Patients With Advanced Ovarian Cancer

A study published on December 21 in the online issue of *The Lancet Oncology* revealed that aflibercept (Eylea, Regeneron Pharmaceuticals), a potent inhibitor of vascular endothelial growth factor (VEGF), shows clinical activity and increases the time to repeat paracentesis for patients with advanced chemoresistant ovarian cancer and recurrent symptomatic malignant ascites. Gotlieb and colleagues assessed the safety and efficacy of aflibercept in the treatment of malignant ascites in a phase II study involving 55 patients with advanced chemoresistant ovarian cancer and recurrent symptomatic malignant ascites. Patients were stratified by the time interval between the 2 most recent paracenteses (≤2 weeks vs >2 weeks), and then randomized to receive either intravenous aflibercept (4mg/kg every 2 weeks; 26 patients) or placebo (29 patients). The double-blind phase of the study continued until repeat paracentesis or for a minimum of 60 days, at which point patients could opt for aflibercept treatment. The primary efficacy endpoint was the time to repeat paracentesis during the double-blind phase. Patients who received aflibercept had a significantly longer mean time to repeat paracentesis than patients in the placebo group (55.1 vs 23.3 days, respectively; 95% CI, 10.6–53.1; *P*=.0019). There were 2 patients from the aflibercept group who did not require a repeat paracentesis during the 6 months of double-blind treatment. The most common grade 3/4 adverse events among the aflibercept group and placebo group, respectively, were dyspnea (6 patients vs 2 patients), fatigue or asthenia (4 patients vs 11 patients), and dehydration (3 patients vs

3 patients). Patients who received aflibercept had a higher frequency of fatal gastrointestinal events (3 intestinal perforations) compared to patients in the placebo group (1 intestinal fistula leading to sepsis). This preliminary study suggests the effectiveness of VEGF blockade in the reduction of malignant ascites, but also confirms the significant clinical risk of fatal bowel perforation in this population of patients with very advanced cancer. The researchers concluded that VEGF blockade should be used with caution in advanced ovarian cancer with abdominal carcinomatosis, and that the benefit-risk balance should be thoroughly discussed with each patient.

ALSYMPCA Trial Demonstrates Survival Benefit of Radium-223 in Patients With Metastatic Castration-Resistant Prostate Cancer

Data from a multicenter, randomized study presented at the 2011 European Multidisciplinary Cancer Congress demonstrated that patients with metastatic castration-resistant prostate cancer (mCRPC) with symptomatic bone metastases who received radium-223 (Alpharadin, Algeta ASA/Bayer Schering Pharma AG) lived 30% longer than those who received a placebo. A total of 922 patients with progressive, symptomatic mCRPC and at least 2 bone metastases were enrolled in the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer investigating Alpharadin) study. Due to ineligibility or refusal, 42% of patients did not receive prior treatment with docetaxel, whereas 58% of patients were either intolerant of the drug or had previously progressed despite docetaxel treatment. A total of 615 patients were randomized to receive 6 injections of 50 kilobecquerel (kBq) per kg radium-223 every 4 weeks, in addition to standard care. There were 307 patients who received a placebo in the same manner, in addition to standard care. According to interim study findings reported by Parker and associates, the median overall survival in the radium-223 group was 14 months, compared with 11.2 months in the placebo group (HR, 0.695; 95% CI, 0.552–0.875; *P*=.00185). Patients who received radium-223 went a median of 13.6 months before developing any skeletal-related events (SREs), compared with 8.4 months for those in the placebo group. The incidence of severe diarrhea or vomiting did not differ significantly between the 2 groups. Respectively, 2% and 4% of radium-223 patients experienced grade 3 and grade 4 hematologic adverse events, compared with 1% and 2% of placebo patients. An Independent Data Monitoring Committee has called for an early cessation of the study, due to the magnitude of benefit and favorable tolerability observed with radium-223. Patients in the placebo arm will be offered treatment with radium-223.

Addition of Gemcitabine to Docetaxel in the Treatment of HER2-Negative Advanced Breast Cancer

In a randomized, phase III study by the Danish Breast Cancer Cooperative Group, Nielsen and colleagues sought to compare the efficacy of gemcitabine plus docetaxel versus docetaxel alone in patients with predominantly human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer. A total of 170 patients received gemcitabine (1,000 mg/m^2) on days 1 and 8 plus docetaxel (75 mg/m^2) on day 8, and 167 patients received docetaxel (100 mg/m^2) on day 1, every 21 days. Time to progression (TTP) was the primary endpoint; secondary endpoints included overall survival, response rate, and toxicity. The median TTP was 10.3 months in the gemcitabine-plus-docetaxel arm, compared with 8.3 months in the docetaxel-alone arm (HR, 0.77; 95% CI, 0.59–1.01; log-rank *P*=.06). A significant difference favoring the gemcitabine-plus-docetaxel treatment arm was shown using the adjusted Cox proportional model for TTP (HR, 0.68; 95% CI, 0.51–0.90; *P*=.007). However, both arms demonstrated similar response rates (gemcitabine plus docetaxel, 36%; docetaxel alone, 34%), and overall survival did not differ between treatment groups (*P*=.57). Grade 3/4 neutropenia occurred in 75% and 69% of patients who received gemcitabine plus docetaxel versus docetaxel alone, respectively. Infections were reported in 26% of patients in the gemcitabine-plus-docetaxel arm versus 21% of patients in the docetaxel-alone arm. Patients who received gemcitabine plus docetaxel had more reports of grade 3/4 thrombocytopenia (16%) than did patients who received docetaxel alone (0.6%), but peripheral neuropathy occurred more often in the docetaxel arm (16% vs 5%, respectively). The study, published online in the November 14 issue of the *Journal of Clinical Oncology*, concluded that no clinically meaningful benefit was demonstrated with the addition of gemcitabine to docetaxel in patients with HER2-negative, locally advanced or metastatic breast cancer.