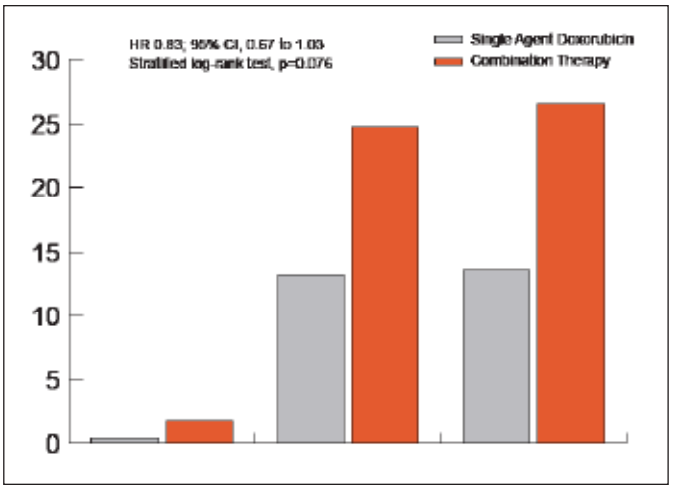
University Nijmegen Medical Center, Nijmegen, Netherlands, compared single-agent doxorubicin (75 mg/m^2) with doxorubicin (75 mg/m^2) plus ifosfamide (7.5 g/m^2) in patients with advanced soft tissue sarcoma (ASTS).

A total of 455 patients with high-grade ASTS were randomized to doxorubicin (n=228) versus doxorubicin plus ifosfamide plus pegfilgrastim (n=227). Patients were stratified according to age, performance status, liver metastases, and histologic grade. The most common histologic diagnoses were liposarcoma, leiomyosarcoma, and synovial sarcoma. The primary endpoint was overall survival (OS). The secondary endpoints were response, toxicity, and treatment-related mortality. The median follow-up was 56 months. An improvement in survival was defined as clinically significant if 1-year survival was at least 10% higher in the combination arm, corresponding with an HR <0.737. Allocated treatment was started by 217 patients in the doxorubicin arm and 215 patients in the combination arm.

There was no significant difference in OS with doxorubicin versus combination treatment (HR, 0.83; 95.5% CI, 0.67 to 1.03; p=0.076; Figure 1). At 1year, OS was 51% in the doxorubicin arm versus 60% in the combination arm. The median OS was 12.8 months with single-agent doxorubicin versus 14.3 months with combination treatment. Progression-free survival (PFS) was significantly better in the combination arm compared with the doxorubicin arm (HR, 0.74; 95% CI, 0.60 to 0.90; p=0.003). The median PFS was 4.6 months with single-agent doxorubicin versus 7.4 months with doxorubicin plus ifosfamide. Patients treated with single-agent doxorubicin versus the combination had a complete response rate of 0.4% versus 1.8%, partial response rate of 13.2% versus 24.7%, and overall response rate of 13.6% versus 26.5%, respectively (Figure 1).

Patients treated with doxorubicin plus ifosfamide versus single-agent doxorubicin had considerably higher rates of grade 3 or higher adverse events, including neutropenia (41.5% vs 37.2%), leukopenia (43.3% vs 17.9%), febrile neutropenia (45.9% vs 13.5%), anemia (34.9% vs 4.6%), and thrombocytopenia (33.5% vs 0.4%), respectively. A total of 121 patients in the doxorubicin arm versus 109 patients in the combination arm discontinued treatment because of progression of disease (PD) or death from PD (41.7% vs 20.7%); toxicity, including toxic death (2.6% vs 17.6%); patient refusal (1.8% vs 4.4%); death not related to malignant disease or toxicity (1.8% vs 0.4%); and other reasons (5.3% vs 4.8%), respectively.

Figure 1. Response Rates with Single Agent Versus Combination Therapy.



Doxo=single-agent doxorubicin; Dxlf=doxorubicin plus ifosfamide.

The combination of doxorubicin and ifosfamide doubled the response rate and significantly improved PFS but did not significantly improve OS in patients with high-grade ASTS. Doxorubicin combined with ifosfamide was considerably more toxic than single-agent doxorubicin. The investigators concluded that single-agent doxorubicin should remain the standard treatment for this population.

The Efficacy and Safety of Docetaxel plus Prednisone with or Without Lenalidomide in Patients with Castrate-Resistant Prostate Cancer: The MAINSAIL Trial

Written by ***Phil Vinall***

Lenalidomide, has been used to treat myeloma and myelodysplastic syndrome. When used in combination with docetaxel and prednisone, or as a single agent, it has been shown to demonstrate activity and tolerability in patients with castrate-resistant prostate cancer (CRPC) [Petrylak DP et al. *J Clin Oncol* 2009]. Daniel P. Petrylak, MD, Yale Cancer Center, New Haven, Connecticut, USA, reported results from the Study to Evaluate Safety and Effectiveness of Lenalidomide in Combination with Docetaxel and Prednisone for Patients with Castrate-Resistant Prostate Cancer [MAINSAIL; NCT00988208] trial, which showed that the addition of lenalidomide to docetaxel and prednisone did not improve overall survival (OS) in CRPC patients and its use was associated with greater toxicity.

This Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of docetaxel plus prednisone as first-line treatment for CRPC. Chemotherapy-naïve patients with progressive metastatic CRPC (effective castration defined as serum testosterone levels <50 ng/dL) and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score ≥2 were randomized to either lenalidomide (25 mg on Days 1 to 14) plus docetaxel (75 mg/m^2 on Day 1 of each cycle) plus prednisone (5 mg BID on Days 1 to 21) or placebo plus docetaxel plus prednisone at similar doses and scheduling. Treatment phase was 21-day cycles until disease progression. Follow-up for survival occurred every 90 days for up to 5 years following study treatment discontinuation. The primary study endpoint was OS. Secondary endpoints included progression-free survival (PFS), objective response, and safety. Patient enrollment was completed in November 2011, with a total of 1059 patients. The data analysis results were based on the cutoff date of January 13, 2012.

The lenalidomide (n=533) and placebo (n=526) arms were well balanced; mean age was 69 years, and ECOG PS scores were 0 in 48.1% and ≥1 in 51.8% of patients. About 71% of patients had radiographic disease progression. Metastatic sites included bone, soft tissue, and both bone and soft tissue. Median OS and PFS were 77 and 45 weeks in the lenalidomide arm, compared with median not reached (HR, 1.53; 95% CI, 1.17 to 2.00; p=0.0017) and 46 weeks (HR, 1.32; 95% CI, 1.05 to 1.66; p=0.0187; in the placebo arm, respectively. Objective response rate was 22.1 % for lenalidomide versus 24.3% for the placebo arm (p=0.3975). The median number of cycles administered were 6 and 8 in the lenalidomide and placebo arms, respectively. All dose reductions were due to adverse events, except for 2 dose reductions of docetaxel that were due to other reasons.

The most common grade ≥3 adverse events that occurred significantly more often in the lenalidomide group included neutropenia (22%), febrile neutropenia (12%), diarrhea (7%), and pulmonary embolism (6.5%). Significantly more deaths (>28 days from last lenalidomide dose) occurred in the lenalidomide arm (20.8%) compared with the placebo arm (15.0%; p=0.016).

The addition of lenalidomide to docetaxel plus prednisone did not improve OS in patients with CRPC and was associated with greater toxicity. Shorter treatment duration, earlier treatment discontinuation, and lower dose intensity of docetaxel might have contributed to this lack of benefit. Studies to explain the poorer outcome of the lenalidomide arm are under way.

Two Years Versus One Year of Trastuzumab in Patients with Early Breast Cancer

Written by ***Tony Rizzo***

The 2005 results of large randomized trials, including the Trastuzumab in Treating Women with Primary Breast Cancer [HERA; NCT00045032] trial, demonstrated statistically significant disease-free survival (DFS) benefit for 1 year of treatment with trastuzumab compared with observation in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. After 2005, the HERA trial focused on the secondary objective of comparing 2 years of trastuzumab treatment with 1 year of treatment. The results of this analysis were presented by Richard D. Gelber, MD, PhD, International Breast Cancer Study Group Statistical Center, Boston, Massachusetts, USA.

A total of 5102 patients with HER2-positive invasive early breast cancer were randomized after adjuvant treatment to observation (1698), 1 year of trastuzumab (n=1703), or 2 years of trastuzumab (n=1701). Patients in the observation group had the option to switch to trastuzumab in 2005. Patients included in the 2 years (n=1553) versus 1 year (n=1552) of trastuzumab analysis were those who remained disease-free for at least 366 days from randomization. For the safety analysis, primary cardiac events were defined as NYHA Class III/IV plus left ventricular ejection fraction (LVEF) <50% and ≥10% below baseline, or cardiac death. Secondary cardiac events were defined as LVEF <50% and ≥10% below baseline, excluding patients with a primary cardiac event.

At 8 years of median follow-up, DFS rates were 75.8% in the 2-year group versus 76.0% in the 1-year group (HR, 0.99; 95% CI, 0.85 to 1.14; p=0.86). DFS was not significantly different with 2 years versus 1 year of trastuzumab in either hormone receptor-positive (76.1% vs 77.2%; HR, 1.05; 95% CI, 0.85 to 1.29; p=0.67) or -negative (75.4% vs 74.7%; HR, 0.93; 95% CI, 0.76 to 1.14; p=0.51) patients. OS rates at 8 years of median follow-up were 86.4% with 2 years of treatment versus 87.6% with 1 year of treatment (HR, 1.05; 95% CI, 0.86 to 1.28; p=0.63).

In the safety analysis population, grade 3/4 adverse events (AEs) were reported in 20.4% of the 2-year group (n=1673), 16.3% of the 1-year group (n=1682), and 8.2% of the observation group (n=1744). Fatal AEs occurred in 1.2% of the 2-year group, 1.1% of the 1-year group, and 0.4% of the observation group. Primary cardiac events occurred in 1.0% of the 2-year group, 0.8% of the 1-year group, and