increased investigator-assessed progression free survival (PFS) over letrozole alone (8.2 vs 3.0 mo, HR = 0.71 (0.53, 0.96) P = 0.019) for women with endocrine sensitive, HER2+ (ErbB2+), previously untreated MBC. Two sub-populations within the HER2+ pt cohort were examined in retrospective analyses: presence of baseline liver metastases and ⩾3 baseline metastatic organ sites.
Methods: 1286 pts were randomized to letrozole/lapatinib or letrozole/placebo. HER2+ was defined by a positive FISH ratio (>2.0) or by immunohistochemistry 3+. Investigator-assessed PFS in these subpopulations were analyzed using Kaplan-Meier with stratified log rank to compare treatment arms within each subgroup: pts with baseline liver metastasis (n = 71) and pts with ⩾3 baseline metastatic organ sites (n = 89).
Results: Pts with HER2 amplified breast cancer who had baseline liver metastasis derived a greater PFS benefit with combination lapatinib and letrozole: 2.7 to 4.4 mo, HR = 0.39 (0.23, 0.65), P ⩽ 0.001. Combination therapy for pts with ⩾3 baseline metastatic organ sites prolonged median PFS from 2.7 to 8.0 mo, HR = 0.59 (0.37, 0.94), P = 0.015.
Conclusions: These retrospective data provide further evidence of the effectiveness (prolonged PFS) of the oral lapatinib/letrozole combination in HER2 amplified, endocrine sensitive metastatic tumors in pts with visceral burden or higher number of metastases.

5078 POSTER

Treatment of leptomeningeal involvement of breast cancer with high-dose methotrexate and ifosfamide

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Background: Leptomeningeal spread in solid tumors has a poor prognosis. Intrathecal chemotherapy and radiation are symptomatic therapeutic approaches. Systemic chemotherapy with blood-brain-barrier crossing agents might be beneficial regarding its potential to treat concomitant brain metastases and systemic disease. In a pilot trial we treated patients with meningeal spread of breast cancer (BC) with high-dose methotrexate and ifosfamide (HDMTX/IFO).
Methods: From July 2007 all consecutive BC patients with leptomeningeal involvement and creatinine clearance >50 ml/min have been treated with 4 g/m^2 MTX as a 4 h infusion on day 1 (with dose adjustment for creatinine clearance and leucovorine rescue starting after 24 hours) and 1.5 g/m^2/day IFO as a 3 h infusion on days 3−5. Treatment was continued for a maximum of 8 cycles.
Results: Three female patients aged 59, 62 and 65 years have been treated thus far. All had concomitant systemic metastases (bone and liver), two patients had been pretreated with up to four systemic chemotherapy regimens. Presenting symptoms were hemi- and paraparesis, radicular pain and multiple cranial nerve palsies. In the first patient chemotherapy was stopped after two cycles due to renal toxicity CTC 2º. She remained neurologically stable for 1.5 months and then received intrathecal chemotherapy followed by six cycles of systemic chemotherapy with topotecan and ifosfamide. She was neurologically improved eleven months after start of HDMTX/IFO. Two patients received six and seven cycles chemotherapy and markedly improved neurologically with stable systemic disease. Time to neurological progression was 5.5 and 7.0 months and overall survival was 8.3 and 11.0 months, respectively.
Further grade 3 or 4 toxicities were thrombopenia 3º in one and leucopenia 3º in two patients.
Conclusion: Systemic chemotherapy with HDMTX/IFO is feasible and active in leptomeningeal involvement of BC. Further improvement may be achieved by additional intrathecal therapy. Liposomal cytarabine has demonstrated impressive activity in malignant leptomeningeal disease. Therefore we initiated a multicenter phase II trail combining systemic HDMTX/IFO and intrathecal liposomal cytarabine in BC patients with meningeal +/− brain relapse.

5079 POSTER

Role of paclitaxel in neoadjuvant chemotherapy in stage IIA-IIIA breast cancer

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Background: Neoadjuvant chemotherapy with doxorubicine and cyclophosphamide in **stage IIA-IIIA** breast cancer has a proven importance. In order to analyze the impact of adding paclitaxel to this regimen, a prospective study was designed in 2004.
Methods: The studied lot consisted in 124 patients admitted in the Oncology Clinic of Craiova, Romania between February 2004 and March 2009. The most important eligibility criteria were: stage IIA-IIIA breast carcinoma, her-2/neu negative, measurable disease and an ECOG performance status of 0 or 1. Patients were randomized 1:1 in order to receive the standard regimen (doxorubicine 60 mg/sqm, cyclophosphamide 600 mg/sqm;) – group A, or paclitaxel plus standard regimen (doxorubicine 60 mg/sqm, cyclophosphamide 600 mg/sqm and paclitaxel 200 mg/sqm;) – group B. Both regimens were administered in cycles repeated every 21 days. If partial response occurred after 2 cycles, patients undertook surgical treatment without further chemotherapy; if not, they were administered a total of 4 cycles, followed by surgery. Stratification criteria were: age, staging, involvement of axillary lymph nodes and hormonal receptors status. Primary endpoints of the study were the response rate for each arm of the study and the quality of life in each group; the latter was assessed using a specific questionnaire.
Results: 124 patients were randomized between February 2004 and March 2006: 62 in group A and 62 in group B. The groups were well balanced regarding the stratification criteria. A significant difference was found between response rates in the 2 groups: partial response rates were 64.51% in group B compared to only 51.62% in group A, while complete response occurred only in group B (1.61%). The remainder of the patients had stationary disease after the regimens: 33.87% of group A and 48.39% of group B. The odds ratio for developing a partial response after the triple association regimen compared to the double association one was 1.25:1. We observed significant toxicities for triple association regimen when compared with standard regime: 34% of grade 3 neutropenia versus 15% and 15% peripheral neuropathy versus 3%.
Conclusions: Despite the higher incidence of neutropenia in the triple association regimen, the higher response rate recommends it as neoadjuvant chemotherapy for stage IIA-IIIA breast cancer.

5080 POSTER

Safety and tolerability of fulvestrant high-dose (500 mg) in postmenopausal women with hormone receptor positive advanced breast cancer

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Background: Two open-label, multicenter Phase II trials, NEWEST (9238IL/0065) and FIRST (9238IL/0006), have shown improved biological and clinical efficacy with fulvestrant high-dose regimen (HD; 500 mg/month + 500 mg on day 14 of month 1) compared with fulvestrant approved-dose (AD, 250 mg/month) and anastrozole, respectively, in either the neoadjuvant and first-line setting in women with hormone receptor-positive advanced breast cancer. Here, safety and tolerability data are presented.
Material and Methods: NEWEST: 211 patients were randomised to fulvestrant HD (n = 109) or AD (n = 102) for 16 weeks prior to curative surgery. At 16 weeks, AEs, endometrial thickness, and serum bone markers were compared with baseline-data. FIRST: 205 patients were randomised to fulvestrant HD (n = 102) or anastrozole (n = 103) as first-line therapy until progression or withdrawal due to an AE.
Results: NEWEST: Incidence rates for any AE (irrespective of causality) were comparable in both groups (72.9% for fulvestrant HD vs. 69.3% for fulvestrant AD), with injection site pain being most common within the HD-group and hot flashes within the AD-group. SAEs other than death occurred in 13.1% in the HD-group and in 11.9% in the AD-group; 0.9% vs. 3% were judged as treatment-related. AEs leading to withdrawal of treatment were rare (0.9% for fulvestrant HD vs. 1% for fulvestrant AD). No adverse effects on endometrial thickness or serum bone markers were identified in either group. FIRST: Incidence rates for any AE were comparable in both groups (70.3% vs. 69.9%) as were incidence rates for drug-related AEs (29.7% for fulvestrant HD vs. 28.2% for anastrozole). Among drug-related AEs, hot flashes were most common in both groups (7.9% vs. 12.6%). SAEs were rare in both study groups (11.9% vs. 9.7%), including only one patient in the fulvestrant HD group with a drug-related SAE (hypertension). Three patients in each group (3.0% vs. 2.9%) experienced an AE leading to discontinuation of treatment.
Conclusions: The safety profile of fulvestrant HD is comparable with that of fulvestrant AD and anastrozole. Fulvestrant HD was well tolerated and