in each treatment group. Common Toxicity Criteria (CTC) grade 3 (>3.6 to ⩽7.2 mg/dL) or grade 4 (>7.2 mg/dL) serum creatinine was infrequent. In the HCM trial, 2 (2.3%) patients treated with 4 mg zoledronic acid developed grade 3 serum creatinine elevations compared with 4 (4%) patients in the pamidronate group with either grade 3 (n=3) or grade 4 (n=1) serum creatinine. Among breast cancer patients treated with 4 mg zoledronic acid (via 15-min infusion) monthly for up to 25 months (core + extension phase), no patient developed grade 3 or 4 serum creatinine elevations compared with 1 (0.5%) patient with grade 4 serum creatinine in the pamidronate group. This compares favorably with other IV bisphosphonates, including ibandronate. Finally, a patient-preference study demonstrated that zoledronic acid was preferred by 86% of patients compared with 14% who preferred pamidronate.

Conclusions: A 15-minute infusion of zoledronic acid has an overall safety profile comparable with other IV bisphosphonates, which have longer recommended infusion times. The shorter infusion of zoledronic acid provides greater patient convenience and is preferred over pamidronate.

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Distribution of tamoxifen in serum and breast cancer tissue and its effects on sex hormone-binding globulin (SHBG)

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Tamoxifen is a front-line drug in the treatment of breast cancer. Of concern are its serious adverse effects especially when used as a chemopreventive agent. We investigated serum concentrations and the accumulation of tamoxifen and its metabolites in normal breast and breast cancer tissues during different dosing regimens. Frozen samples of serum, normal breast tissue and breast cancer tissues were obtained from patients exposed to 1, 5 or 20 mg tamoxifen daily for 28 days prior to surgery (n=38, 37 and 36 respectively). The concentrations of tamoxifen, 4-hydroxytamoxifen and N-desmethyltamoxifen were analysed by HPLC.

While 35% of the patients used tamoxifen alone, 41% used two or more drugs in addition to tamoxifen. The median (range) of tamoxifen concentrations at doses of 1, 5 and 20 mg daily were in serum (ng/ml) 7.5 (2.9–120.9), 25.2 (1.9–180.9) and 83.6 (8.7–134.4), in normal breast tissues (ng/mg) 100.5 (33.1–694), 218.7 (34.5–601.6) and 866.5 (413.4–1466), and in breast cancer tissues were 78.2 (35.9–184), 272.3 (122–641) and 744.4 (208.6–2556) respectively. Serum and tissue tamoxifen and metabolite concentrations were significantly inter-correlated and were also correlated with changes between baseline and post-treatment levels of SHBG.

In conclusion, we observed a wide range of tamoxifen and metabolite concentrations in each of the three dose groups. The concentrations of tamoxifen and metabolites in serum correlated to the levels in tumour tissues, and the oestrogen agonistic effects of tamoxifen on SHBG increased with increasing tamoxifen concentrations.

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Effects of anastrozole on the lipid profile in postmenopausal breast cancer patients – a preliminary study

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Introduction: Anastrozole, a new generation aromatase inhibitor, has been used to treat postmenopausal metastatic breast cancer, and several clinical trials of adjuvant treatment using this agent are ongoing. However, the effects of anastrozole on lipid metabolism are unknown. We previously reported the effects of tamoxifen on lipid metabolism in clinical and experimental studies (Hozumi et al., J Clin Endocrinol Metab 1998, Hozumi et al., Horm Res 2000). Moreover we reported the effect of anastrozole on lipid metabolism in ovariectomized rats (Hozumi et al., Breast Cancer Res Treat 2003). In the present study, we evaluated the effects of anastrozole on the serum lipid profile in postmenopausal breast cancer patients.

Subjects & Methods: A total of 38 postmenopausal patients, mean age 62.8 (53–79), with breast cancer were treated with anastrozole, 1 mg once daily. After an overnight fasting, serum lipid parameters [total cholesterol, triglycerides, LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), apolipoprotein A1, B and lipoprotein (a)] were measured before treatment and at 3 months afterwards.

Results: A significant increase in total cholesterol (P=0.037), LDL-C (P=0.015), HDL-C (P=0.013) and apolipoprotein A1 levels (P=0.03) in the serum was noticed after anastrozole treatment.

Conclusion: Previously we showed that anastrozole did not affect lipid metabolism in ovariectomized rats. In the present clinical situation, however, anastrozole augmented serum lipid parameters although the investigation was small and preliminary. A new clinical study is underway to compare the effects of anastrozole on lipid metabolism with those of exemestane and tamoxifen.

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Prospective investigation of the significance of cardiac markers, NT-pro Brain Natriuretic Peptide (NT-proBNP) and Troponin T (TnT), in the HERCULES study of epirubicin/cyclophosphamide with or without trastuzumab (Herceptin®)

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Introduction: The Herceptin® trial HO648g demonstrated that the combination of Herceptin® with doxorubicin was efficacious, but associated with a higher than expected incidence of cardiotoxicity. Therefore, the HERCULES trial was initiated to investigate the cardiac safety of epirubicin (E) (60 or 90 mg/m^2) and cyclophosphamide (C) (600 mg/m^2) with or without Herceptin® (H) (given at the standard weekly schedule until disease progression). A secondary endpoint of this trial was to determine the significance of the cardiac markers NT-proBNP and TnT, markers of congestive heart failure (CHF) and myocardial damage, respectively, as predictors of early onset cardiac dysfunction.

Patients and Methods: To date, 75 patients without pre-existing cardiac disease have been entered into the trial and followed for cardiac safety (26 EC60 + H; 25 EC90 + H; 24 EC90 only). Echocardiography was used to assess left ventricular ejection fraction (LVEF) as a measure of cardiac function every 3 weeks during chemotherapy and every 12 weeks thereafter. Serum concentrations of NT-proBNP and TnT were measured in the Herceptin® arm only weekly for the first two chemotherapy cycles and then every 3 weeks until week 43.

Results: Minor drops in LVEF were common and there was large intra-patient variation in LVEF measurements over time. Three cardiac events were reported in the Herceptin®-containing arms: one patient in the EC60 + H arm experienced an asymptomatic decline in LVEF to <50% and two patients in the EC90 + H arm experienced CHF. One additional cardiac event was seen in the in the EC90-alone arm (arrhythmia/tachycardia). No correlation between serum levels of NT-proBNP or TnT and cardiac events could be determined: no significant increases in these markers were observed in the three patients at, or close to, the time they experienced the cardiac event. However, the cardiac events occurred shortly following week 43 and so it is unknown whether cardiac marker levels subsequently increased. Small increases in TnT were seen in nine patients receiving Herceptin® who did not experience a cardiac event. Fluctuations in NT-proBNP, within normal limits, were also noted in many patients who did not experience cardiac events. Neither absolute LVEF values nor changes in LVEF were shown to correlate with clinical symptoms and/or cardiac marker levels.

Conclusions: The preliminary findings from a trial of EC with/without H suggest that NT-proBNP and TnT levels are not a useful indicator of early onset of cardiac dysfunction.

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The possible life-threatening reactivation of hepatitis B during chemotherapy can be prevented by a close monitor of liver function during chemotherapy

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Purpose: To report 18 patients of breast cancer with reactivation of hepatitis B which was proven by both histology and serology during chemotherapy for breast cancer.