during the first three cycles of CT was significantly more frequent in older premenopausal BC pts, than in younger ones. Finally, amenorrhea was permanent, according to the 4 age groups, in 3%, 3.5%, 51% and 73% pts, respectively, while the frequency of temporary amenorrhea decreased with the age from 15% to 9.8%. The number of CT cycles also significantly influenced the frequency of amenorrhea: it occurred in only 22.5% pts who received less than 6 cycles of CT, and in 53.7% of those who received 6 or more than 6 CT cycles. The later result was probably additionally influenced by the cumulative dose of the anthracycline.

In conclusion, amenorrhea induced by anthracycline regimens seems to be less frequent than in non-anthracycline CMF-based regimens. It is rather rare in very young women. These finding could be important in a multiple clinical aspects: from the adjuvant endocrine treatment planning in premenopausal endocrine-responsive BC pts to the prediction of the loss of fertility in BC survivors.

295 POSTER HIGHLIGHT

Lamivudine for the prevention of hepatitis B virus reactivation in hbsag seropositive cancer patients undergoing cytotoxic chemotherapy

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Background: Breast cancer is a rapidly increasing problem in many developing countries and cytotoxic chemotherapy is now an integral part of its management. In several developing countries, the carriage of hepatitis B virus (HBV) in cancer patients may be as high as 12% and such patients are at risk of developing HBV reactivation during chemotherapy, which is a well-described complication resulting in varying degrees of liver damage that may lead to death. In this prospective study, breast cancer patients with chronic HBV infection received the antiviral agent lamivudine prior to chemotherapy, the objectives were to assess the efficacy of lamivudine in reducing the incidence of HBV reactivation, and diminishing morbidity and mortality during chemotherapy.

Methods: The study group consisted of 27 patients who were treated with lamivudine prior to and until 8 weeks after discontinuing chemotherapy (the 'prophylactic lamivudine' group). They were compared with historical controls which consisted of 41 consecutive patients who underwent chemotherapy without prophylactic lamivudine. The outcomes, in terms of the incidence of HBV reactivation and clinical consequences, were compared.

Results: The 2 groups were comparable in most baseline-characteristics, although in the prophylactic lamivudine group, there were significantly more patients receiving anthracyclines (96% vs 51% in the controls, p<0.001). In the prophylactic lamivudine group, there was significantly less HBV reactivation (7% vs 41% in the controls, p=0.003), fewer incidences of hepatitis (11% vs 66%%, p<0.001) that were less severe (7% vs 15%, p=0.117), and less disruption of chemotherapy (26% vs 51%, p=0.02). There was no associated mortality in both groups.

Conclusions: Prophylactic lamivudine significantly reduced the incidence and morbidity of HBV reactivation in breast cancer patients undergoing chemotherapy.

296 POSTER HIGHLIGHT

Long-term safety of zoledronic acid for the treatment of patients with breast cancer and bone metastases

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Background: Zoledronic acid has demonstrated clinical benefit superior to that of pamidronate for the treatment of bone metastases in patients with breast cancer. Moreover, zoledronic acid can be administered via a more convenient 15-minute infusion. However, concerns have been raised regarding the renal safety profile of zoledronic acid. Herein, the renal safety profile of 4 mg zoledronic acid (via 15-minute infusion) is compared with that of 90 mg pamidronate (via 2-hour infusion).

Materials and methods: Patients were randomized to receive zoledronic acid or pamidronate every 3–4 weeks for up to 25 months in a multicenter, phase III trial. Data presented are from the stratified subset of 766 patients with breast cancer. A notable increase in serum creatinine was defined as an increase of ⩾0.5 mg/dL for patients with baseline serum creatinine ⩽1.4 mg/dL, an increase of ⩾1.0 mg/dL for patients with baseline serum creatinine > 1.4 mg/dL, or any increase ⩾2 times baseline value. These are sensitive and conservative criteria for determining elevated serum creatinine.

Results: A total of 454 patients completed the 13-month core phase, and 165 patients completed the 12-month extension phase. Baseline serum creatinine was similar between treatment groups, and approximately 95% of patients had normal serum creatinine (<1.4 mg/dL) at study entry. The renal safety profile of 4 mg zoledronic acid was comparable with that of 90 mg pamidronate at 25 months. Overall, 9.4% of patients treated with 4 mg zoledronic acid versus 6.5% of pamidronate-treated patients experienced notable increases in serum creatinine. However, Common Toxicity Criteria (CTC) grade 3 (>3.6 to ⩽7.2 mg/dL) or grade 4 (>7.2 mg/dL) serum creatinine was infrequent. One (0.5%) patient in the pamidronate group developed CTC grade 4 serum creatinine, whereas no patient treated with 4 mg zoledronic acid developed either grade 3 or 4 serum creatinine. Kaplan-Meier analysis of time to first episode of notable serum creatinine increase also showed that 4 mg zoledronic acid was associated with a slightly increased risk of elevated serum creatinine compared with pamidronate, which was not statistically significant (hazard ratio = 1.401; *P*=0.371).

Conclusions: With long-term use (up to 25 months), 4 mg zoledronic acid (via 15-minute infusion) has a renal safety profile comparable with 90 mg pamidronate (via 2-hour infusion) and other IV bisphosphonates.

297 POSTER HIGHLIGHT

Anastrozole therapy and lipid profile: an update

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Background: Endocrine therapy of breast cancer is aimed at inhibiting estrogen-dependent proliferation of cancer cells. Newly developed aromatase inhibitors suppress estrogens synthesis to undetectable levels. The concern exists they might increase the risk of hypoestrogenemia-related disorders, such as disturbances in lipid profile. The current study updates at the prolonged observation our previous results on effects of anastrozole – III generation aromatase inhibitor – on lipid metabolism in tamoxifen pretreated breast cancer patients.

Material and Methods: the study included 51 postmenopausal breast cancer women (median age: 67 years, range: 45–87), who were converted to anastrozole after tamoxifen treatment (median duration of therapy: 76 weeks, range: 14–193). Concentrations of basic blood lipids and body mass index values (BMI = weight in kilograms divided by squared height in meters) were measured at baseline and three times afterwards: at minimum 24 (median: 26, range: 24–33; N=51), 60 (median: 63, range: 60–70; N=51) and 130 (median: 134, range: 130–147; N=25) weeks of anastrozole administration.

Results: there was no statistically significant change over time in basic lipid parameters, that included total- (p=0.51), LDL- (p=0.61), and HDL-cholesterol (p=0.43), triglycerides (p=0.78), the atherogenic risk ratios: total/HDL-cholesterol (p=0.56) and LDL/HDL-cholesterol (p=0.33) as well as in mean BMI values (p=0.93).

Conclusion: anastrozole used in sequence to tamoxifen for approximately 3 years does not affect lipid profile and BMI values of breast cancer patients.

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Safety and convenience of the 15-minute infusion of zoledronic acid

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Background: Highly potent, new-generation bisphosphonates with clinical activity at extremely low molar doses can be administered using short infusion time without compromising renal safety. Among intravenous (IV) bisphosphonates approved for the treatment of hypercalcemia of malignancy (HCM) or bone metastases in patients with breast cancer, zoledronic acid has the shortest recommended infusion time (i.e., 15 min) compared with 1–2 hrs for other agents. Moreover, zoledronic acid has demonstrated clinical benefit superior or equivalent to that of pamidronate in patients with HCM or breast cancer and bone metastases.

Materials and Methods: The safety profile of zoledronic acid (4 mg via 15-min infusion) was compared with that of 90 mg pamidronate (via 2–hr infusion) based on randomized, comparative trials. Comparisons with other bisphosphonates are based on published reports.

Results: Comparative trials of 4 mg zoledronic acid versus 90 mg pamidronate in patients with HCM (N=287) and breast cancer patients with bone metastases (n=1130) have shown that zoledronic acid has an overall and renal safety profile comparable with pamidronate. Commonly reported adverse events – including fever, nausea, fatigue, constipation, and anemia – occurred in a similar proportion of patients

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.

299 POSTER

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.

300 POSTER

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.

302 POSTER

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.