positive or high-risk (T ⩾ 2 cm). Following the completion of 6 cycles Doc chemotherapy, all patients received 4 cycles Epirubicin 80 mg/m^2 and Cyclophosphamide 600 mg/m^2 every 3 weeks. The starting dose of Doc was 45 mg/m^2, and dose was escalated in increments of 5 mg/m^2 until MTD was reached. Patients were treated in cohorts of three to six per group by using a standard phase I study design. If none of three patients had dose limiting toxicity (DLT) during cycle 1 to 3, Doc dose was escalated to next level. If one or two of three patients had DLT during cycle 1 to 3, then three additional patients were treated at the same dose level. The MTD was considered dose level of three of three patients or more than three of six patients had DLT during cycle 1 to 3. Toxicity was evaluated by NCI-CTC ver2. DLT was defined as febrile neutropenia (fever ⩾ 38^{0}C and grade 3 to 4 neutropenia), grade 4 neutropenia, grade 3 to 4 thrombocytopenia, grade 3 to 4 nonhematologic toxicity (except nausea, vomiting, fatigue, and anorexia), or administration interval more than 3 weeks.

Results: DLT was not reached until Doc 65 mg/m^2 level. However, three DLTs were observed to five patients on 70 mg/m^2 level, and MTD of biweekly Doc was 65 mg/m^2.

Conclusions: Doc 65 mg/m^2 was selected as the phase II recommended dose. We plan a phase II clinical study of sequential administration of biweekly Doc followed by EC chemotherapy as preoperative chemotherapy in high-risk breast cancer patients.

400 PUBLICATION

Sentinel node biopsy and axillary node sampling in women with breast cancer undergoing breast conserving surgery. Preliminary results of a prospective study

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Background: Axillary dissection still represents the most accurate means of determining axillary lymph node status in patients with breast cancer (BC), but at the expense of significant morbidity. However, sentinel node biopsy (SNB) technique does not reach 100% sensitivity in detecting (or excluding) axillary node metastases, especially in the presence of unsuspected micrometastases. The aim of this study was to asses the accuracy of axillary node sampling (ALNS) in addition to SNB in patients with BC undergoing curative surgery.

Patients and methods: Sixty-seven consecutive women (median age 54 years, range 28–68 years) with pT1 primary BC undergoing breast conserving surgery were enrolled in the study. Patients were prospectively randomizes to undergo SNB alone (Group A, 35 patients) or ALNS in addition to SNB (Group B, 32 patients), followed by level I-II axillary dissection. In all cases, a combined method using radioisotope and blue dye was used for SNB. Patients with positive SNB were excluded.

Results: The age of the patients (54.8±8.2 vs. 54.1±9.2, p = 0.74) and the number of the removed nodes (median 19, range 16–25 in each Group) did not differ significantly (p = NS) between Groups. A median of 7 lymph nodes (range 6–9) was removed in Group B patients. In all patients intraoperative frozen section examination did not show positive nodes, whilst final histopathology showed micometastases in six (8.9%) patients. The sensitivity of SNB technique alone (false-negative rate: 14.3%) and SNB in addition to ALNS (false-negative rate: 3.1%) was 85.7% and 96.9%, respectively.

Conclusions: SNB alone in inaccurate in detecting axillary node micrometastases, and ALNS should be performed in all patients with macroscopically suspicious nodes and negative SNB.

401 PUBLICATION

Concomitant weekly tumour bed boost with whole breast irradiation in patients with locally advanced breast cancer undergoing breast conservation therapy: a prospective study

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Aim: To evaluate prospectively the feasibility of concomitant weekly tumour bed electron boost along with whole breast radiotherapy following breast-conserving therapy (BCT) in patients with locally advanced breast cancer (LABC) with the aim of reducing treatment duration by 1week.

Methods: Thirty patients with LABC suitable for BCT following neoadjuvant chemotherapy were eligible for the study. Conventional bilateral tangential photon fields to the whole breast and a direct supraclavicular field was delivered every day from Monday to Friday for 25 fractions to a dose of 50 Gy. In addition, an electron boost to the tumour bed was delivered every Saturday, delivering 5 such weekly fractions to a boost dose of 12.5 Gy. During radiotherapy (RT), patients were evaluated every week and skin reactions recorded as per CTC criteria. Cosmesis was recorded as per 4 point EORTC breast cosmetic score by two clinicians independently blinded to each other before RT and at 6 month follow up. This prospective cohort of 30 patients (Concomitant Boost [CB group]) was compared to a similar cohort of 32 patients treated conventionally with tumour bed boost of 15 Gy/6# given after the completion of whole breast irradiation (Conventional Radiotherapy [CRT group]).

Results: Chemotherapy achieved a complete clinical response in 25 (40%) patients, partial response in 33 (53%) patients and pathological complete response in 12 (19%) patients. Median interval between lumpectomy and the start of RT was 87 days (range, 31 to 163 days). All patients completed RT as planned. No patient in either group developed Grade IV skin toxicity. At conclusion of RT, in the CB group, one patient (3.3%) developed confluent moist desquamation (Grade III) in the tumour bed region and 3 (10%) developed this outside the tumour bed region. In the CRT group, 2 and 4 patients (6.3%) developed moist desquamation in and outside the tumour bed region respectively. The median duration of radiation was 35 days (range, 32–40 days) in CB group patients and 45 days (range, 41–55 days) in CRT group patients. Although the cosmetic outcome was significantly worse at 6 month post RT as compared to baseline pre RT evaluation in some domains (skin colour, p = 0.001, location and shape of nipple, p = 0.004), it was not significantly different in the two groups.

Conclusion: Concomitant tumour bed boost along with whole breast RT appears to be safe and feasible in a select group of patients. Moreover it can be completed earlier by a median of 10 days than conventional practice, which can have favourable human and machine resource implications.

402 PUBLICATION

Toremifen is a more desirable component of standard treatment of breast cancer than Tamoxifen

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Background: Estrogens are acknowledged as an important pathogenetic element of the development of breast cancer. Blocking of estrogen receptors results in an improvement of the prognosis and reduction of breast cancer mortality. Toremifen and Tamoxifen are the common agents blocking estrogen receptors. However, Tamoxifen, unlike Toremifene, has genotoxic and oncogenic effects, which are due not merely to hydrooxidation of Tamoxifen.

Material and methods: We have studied the effects of Toremifen and Tamoxifen on the hormonal homeostasis of 52 patients with stage 2 breast cancer by using RIA with 'Immunotech' kits in order to determine the serum levels of follicle-stimulating hormone (FSH), luteinising hormone (LH), estrogen and progesterone in 3 and 6 months following the beginning of administration of Toremifen or Tamoxifen. Estrogen and progesterone receptors were determined by using standard enzyme-linked immune assays.

Results: Toremifen effects have been shown to be more favourable on the pathogenetic level: estrogen levels havetripled by month 6 of treatment with Tamoxifen, whereas estrogen levels have only doubled by month 6 of treatment with Toremifen. FSH levels were lowering upon administration of either of the studied drugs, however, upon administration of Tamoxifen, FSH levels were reduced by 1/3, whereas upon administration of Toremifene – by 4 times, which testified to Toremifen superiority on the pathogenetic level. Five-year follow-up of 21 patients taken the mentioned drugs have shown positive results of administration of Toremifene in both receptor-negative and receptor-positive patients.

Conclusions: Accounting for the aforementioned facts and the general oncogenicity of Tamoxifen, we suggest Toremifen to be a more suitable component of the standard treatment of breast cancer.

Poster presentations (Mon, 31 Oct)
Breast cancer – advanced disease

403 POSTER

The amino-terminal propeptide (PINP) of type I collagen is a clinically valid indicator of bone turnover in osseous metastatic breast cancer while osteocalcin and CTX show inferior monitoring performance

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Background: Efficacy control of any treatment of metastatic spread to the bone in breast cancer is difficult and usually initiated later than restaging of visceral – or soft tissue metastases. The amino-terminal propeptide (PINP)

of type I collagen as a biochemical indicator of bone turnover might facilitate an early and valid disease surveillance. We investigated the utility of total PINP in breast cancer patients at different stages of the disease with and without bone metastases to monitor the response to therapy in relation to the serum level of PINP. The results were compared to osteocalcin and ß-carboxyterminal telopeptide (CTX) or crosslaps concentrations as historically used markers for bone metabolism, while CA15−3 was used as reference mass tumor marker.
Materials and methods: Baseline serum samples of 51 patients with metastastic breast cancer under systemic therapy were investigated. A total of 11 patients with primary breast cancer under neoadjuvant chemotherapy were used as control collective without bone spread. In total; 38 patients had been diagnosed with bone metastases while 24 had no evidence of metastastic spread to the bone. All patients with bone spread received bisphosphonates in addition to systemic treatment. Osteocalcin, CTX and PINP levels were measured on the Elecsys® 2010 analyzer (electro-chemiluminescence immunoassay – ECLIA). Cut-offs of normal were as follows: Osteocalcin: 41.3 pg/ml; CTX: 1008 pg/ml; PINP: 95 ng/ml, CA15−3: 28 U/ml. Patients were grouped based on overal treatment outcome in responders (CR/CR), stable disease (SD) and primary progression (PD).
Results: ROC analysis of osseous versus non-osseous metastatic disease revealed an area under the curve (AUC) for PINP of 0.75. The ROC result was much worse and therefore not discriminative for CTX (0.56) and osteocalcin (0.58). In our study we found no difference for the baseline levels of PINP, CTX and osteocalcin between post- and premenopausal women ($p > 0.5$ each). Patients with bone metastases showed statistically significantly higher PINP levels at baseline and at progression in comparison to patients without bone metastases at both time points ($p = 0.02$).
Conclusions: PINP concentrations can discriminate patients with bone metastases from those without osseous spread much better than osteocalcin or CTX. Further data on monitoring of patients with metastatic breast cancer and bone metastases as compared to patients without bone metastases (= bone specific monitoring) will be presented.

404 POSTER

Effect of intravenous and oral ibandronate on the need for analgesic interventions for metastatic bone pain: phase III trial results

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Background: Bone metastases often cause severe pain and considerable disability, which is managed most commonly with radiotherapy and/or opioid analgesics. As potent inhibitors of osteoclast-mediated bone resorption, bisphosphonates reduce skeletal-related event (SRE) rates and can also relieve metastatic bone pain. Here, we present supportive pain efficacy data from phase III trials of intravenous and oral ibandronate in breast cancer patients with bone metastases.
Materials and methods: Three 96-week, randomized, double-blind, placebo-controlled trials were conducted. In a trial of intravenous ibandronate, a 6mg dose ($n = 154$) was compared with placebo ($n = 158$) infused over 1−2 hours every 3−4 weeks. In two trials of oral ibandronate, a 50 mg daily dose ($n = 287$) was compared with placebo ($n = 277$) (prespecified pooled analysis). Bone pain was measured on a 5-point patient-rated scale from 0 (no pain) to 4 (intolerable). The requirement for radiotherapy was recorded as part of SRE monitoring. Analgesic use was measured on a 7-point scale from 0 (none) to 6 (requiring ⩾100mg morphine [or equivalent] daily).
Results: Both intravenous and oral ibandronate significantly reduced pain scores below baseline throughout 2 years of therapy (mean change at endpoint: 6mg –0.28 vs placebo +0.21, $p < 0.001$; 50 mg −0.10 vs placebo +0.20, $p = 0.001$). The incidence of events requiring radiotherapy was significantly lower in ibandronate-treated patients at endpoint (6 mg 0.91 vs placebo 1.09, $p = 0.011$; 50 mg 0.73 vs placebo 0.98, $p = 0.011$). Mean change from baseline in analgesic use score at endpoint was also lower in the ibandronate groups (6 mg 0.51 vs placebo 0.90; 50 mg 0.60 vs placebo 0.85); the between-groups difference was statistically significant for oral ibandronate ($p = 0.019$ vs placebo).
Conclusions: Both intravenous and oral ibandronate significantly reduced bone pain even with the concurrent reduction in the use of analgesics and radiotherapy. This suggests that pain relief was not due to these factors and ibandronate was responsible for pain palliation. Ibandronate offers the flexibility of effective intravenous and oral formulations to treat metastatic bone pain and other SREs.

405 POSTER

Phase III trial of oral ibandronate and intravenous zoledronic acid in breast cancer patients with bone metastases: comparison of bone turnover markers

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Background: There is a correlation between levels of bone turnover markers and the incidence of skeletal-related events in patients with metastatic bone disease. Ibandronate is a single-nitrogen bisphosphonate available in intravenous and oral formulations with similar efficacy. In this head-to-head, multicenter, randomized, open-label, parallel-group study, oral ibandronate was compared directly to intravenous zoledronic acid with respect to biochemical markers of bone turnover.
Materials and methods: Breast cancer patients with advanced disease and at least one confirmed osteolytic or mixed bone lesion received oral ibandronate 50 mg/day ($n = 128$) or intravenous zoledronic acid 4 mg ($n = 126$) infused over 15 minutes every 4 weeks for 12 weeks. The primary endpoint was the mean percentage change in serum levels of cross-linked C-terminal telopeptide of type I collagen (S-CTX) at the end of the study. Other assessments included urinary CTX (U-CTX), and serum levels of bone specific alkaline phosphatase (BAP), amino-terminal procollagen propeptides of type I collagen (P1NP), and osteocalcin (OC).
Results: Treatment with ibandronate or zoledronic acid was associated with comparable reductions in all bone turnover markers at study endpoint (Table 1).

Table 1: Mean (CI) percentage change from baseline in bone turnover markers

	S-CTX*	U-CTX	BAP	P1NP	OC
Ibandronate	−76 (−81 to −71)	−76 (−83 to −69)	−37 (−43 to −30)	−47 (−55 to −40)	−35 (−39 to −30)
Zoledronic acid	−73 (−81 to −65)	−82 (−87 to −77)	−26 (−43 to −8)	−39 (−52 to −26)	−26 (−43 to −8)

*Baseline S-CTX levels in the treatment groups were ibandronate 0.65 ng/ml and zoledronic acid 0.70 ng/ml

Conclusion: In this head-to-head trial, oral ibandronate was statistically non-inferior to intravenous zoledronic acid for the primary endpoint of S-CTX. Both agents also had similar effects on U-CTX and serum levels of BAP, P1NP and OC. Overall, a convenient oral ibandronate dose of 50 mg/day is as effective as intravenous zoledronic acid in suppressing tumor-induced bone resorption, suggesting comparable efficacy for the prevention of skeletal-related events (SREs). Head-to-head studies comparing SRE rates are warranted to confirm results.

406 POSTER

Safety and efficacy of sunitinib malate (SU11248) as second-line therapy in metastatic breast cancer (MBC) patients: preliminary results from a Phase II study

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Introduction: Sunitinib malate is an oral multitargeted tyrosine kinase inhibitor of VEGFR, PDGFR, KIT and FLT3. Angiogenesis and proliferation of breast cancer are stimulated by autocrine and paracrine signalling involving VEGFR and PDGFR. Results are reported from a Phase II trial of sunitinib in MBC patients (pts) unresponsive to prior therapy.
Materials and methods: This open-label, multicentre, Phase II study enrolled female pts with unresectable histologically/cytologically confirmed breast adenocarcinoma and failure of prior anthracycline (A) or taxane (T) therapy (progression during or within 12 months of an A or T therapy in the adjuvant and/or MBC setting). In addition, pts were required to have measurable disease, ECOG PS of 0/1 and adequate organ function. Pts received sunitinib 50 mg q.d. orally for 4 weeks, followed by 2 weeks without treatment to comprise a 6-week cyclical regimen. Toxicity-related dose reduction was permitted. The primary endpoint was objective response rate (ORR), assessed every two cycles by RECIST. A total sample size