11 Proffered Paper Oral

Internation breast cancer intervention study I: updated side effects analysis

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Background: Tamoxifen is an effective drug, both for preventing and treating breast cancer, but its role in prevention is limited by its side effect profile, particularly related to endometrial problems and thrombotic events. In the IBIS-I study, 7154 women at increased risk of breast cancer were either randomised to tamoxifen 20 mg/day or placebo for 5 years.

Methods: Women in the IBIS-I study gave detailed information of specific side effects at each 6 monthly follow-up visit. Gynaecological, vasomotor symptoms and other factors were evaluated according to follow-up time, severity and use of hormone replacement therapy. In addition, non-breast related cancer deaths have been updated. Here, we will present updated results on side effects and deaths incorporating four additional years of follow-up.

Results: After a median of 84 months follow-up, 95.4% of women had completed their active treatment. Very large numbers of side effects were reported by participants in both treatment arms. However, the only major categories that showed significant differences were vasomotor and gynaecological side effects which were about 12% higher in the tamoxifen group than the placebo group. There were higher proportions of hot flushes, irregular bleeding, vaginal discharge, and vaginal thrush in the tamoxifen group whereas breast complaints reports were about 27% lower in the tamoxifen group than in the placebo group (607 vs. 830, $P < 0.0001$). In particular, breast diseases such as cysts (99 vs. 221, $P < 0.0001$) and breast pain (162 vs. 242, $P < 0.0001$) were reduced in the tamoxifen group. The occurrence of nail changes, particularly brittle nails, were higher in the tamoxifen group (171 vs. 111, $P = 0.0003$). To date, no significant differences had been found for osteoporotic, non-osteoporotic fractures, cataracts or any other eye problems between the two treatment groups. All cause mortality was non-significantly higher in the tamoxifen group (54 vs. 44, $P = 0.24$). The relative excess is smaller since our first report (25 vs. 11).

Conclusions: The updated IBIS-I side effects analysis shows no new adverse events and no increased death rate is found with tamoxifen. Although very large numbers of side effects were reported, tamoxifen was well tolerated and no new safety concerns were identified.

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Zoledronic acid in the prevention of cancer treatment-induced bone loss in postmenopausal women receiving letrozole as adjuvant therapy for early breast cancer (ZO-FAST study)

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Rationale: Letrozole has been demonstrated to be safe and effective in the treatment of early receptor positive breast cancer in post-menopausal women, reducing the risk of recurrences by 19% as early adjuvant therapy, and by 42% in the extended adjuvant setting. Like other aromatase inhibitors (AIs), long-term letrozole is associated with loss of bone mineral density (BMD). Defining the role of bisphosphonates is becoming more important with the increased use of AIs as adjuvant therapy for 3 to 5 years or longer. Zoledronic acid, a potent bisphosphonate, has been shown to prevent BMD loss in premenopausal patients on adjuvant estrogen-suppression therapy. ZO-FAST was designed to investigate the optimum timing of zoledronic acid with adjuvant letrozole (2.5 mg/d for 5 yrs) in postmenopausal women.

Methods: Patients are randomized between zoledronic (4 mg IV q 6 months) starting at initiation of letrozole versus delayed zoledronic acid (i.e. when T score decreases < −2 SD below normal, or in the case of non-traumatic fracture). Change in lumbar spine BMD is the primary endpoint. Clinically significant bone loss was defined as: 6% reduction in BMD per year, cumulative reduction of 8% over any period of time, BMD < −2.5 SD, and fracture or impending fracture on x-ray.

Results: 1066 patients have been recruited by 112 centers in 28 countries. Patients by stratification factors: prior adjuvant chemo-therapy: yes: 573; no: 493. Baseline BMD T score: > −1 SD: 718; −1 to −2 SD: 348. Median age (range): 58 (37–87) yrs. The most common side effect reported is arthralgia (21.3%). 90 (8%) patients have been withdrawn from the study as of November 2005, with only 42 (4%) patients withdrawing due to adverse events. Safety data trends including summaries by treatment arm will be presented at the meeting. Data lock is planned for January 2006.

First results on safety, 12 Month BMD and the number of patients on the delayed arm who met the criteria for starting Zometa will be available at that time and the data will be presented at the meeting.

Conclusions: ZO-FAST, along with the companion protocol Z-FAST, will offer important insights into the prevention and treatment of aromatase inhibitor related bone loss and help the medical community define the best strategy of addressing this issue by combining the aromatase inhibitor letrozole with zoledronic acid in early breast cancer.

Wednesday, 22 March 2006 14:15–16:00

SCIENTIFIC SESSION

Imaging

13 Invited

PET in the axilla

Abstract not received.

14 Invited

Breast cancer diagnosis – when is MRI indicated?

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Introduction: Breast MRI has proven to be the most sensitive method for detection of invasive breast cancer and for complementing mammography in the detection of DCIS. Due to its limited specificity, the difficult localisation of lesions visible by MRI alone and its high costs, indications need to be well selected.

Procedure and Results: MR technique is meanwhile well established and appropriate recommendations exist in the literature.

Indications, which are considered for breast MRI include:

- local staging before breast conservation in the difficult-to-assess breast;
- high risk patients;
- search for primary tumor (CUP-syndrome);
- diagnostic problems in patients with silicon implants or in patients with scarring after breast conservation;
- monitoring of therapy;
- very selected diagnostic problems which cannot be solved by conventional imaging.

An overview of the present literature is provided. To date the level of evidence for most indications is "3". Randomized studies and studies concerning long-term outcome are needed.

Conclusion: MRI can provide valuable additional information. In order to minimize unnecessary false alarm and work-up, MRI should be strictly limited to appropriate indications. It should be performed in breast centers where high experience with conventional, interventional and MR breast imaging is available, where an interdisciplinary team is present and where systematic documentation of the results and regular feed-back is guaranteed.

15 Invited

Monitoring response to therapy with imaging

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Neoadjuvant chemotherapy (NC) has become popular for patients with advanced breast cancer or operable cancers. The advantages of this systemic therapy serves as an in vivo sensitivity test, increases the rate of breast conserving surgery and facilitates the study of cancer biology. In addition, the pathological response of tumours to NC appears to be a surrogate marker for patient outcome. Besides clinical examination, breast imaging is used to evaluate the shrinkage of tumours under treatment and determine responders. Mammography allows detection of malignant microcalcifications that is poorly responsive to NC. The combination of physical examination with either mammography or ultrasound significantly

improves the accuracy of noninvasive assessment of tumour dimensions. Ultrasound is the best predictor of size for axillary lymph nodes. Magnetic resonance imaging (MRI) is the most accurate imaging modality for the assessment of tumour response (size), the detection of multifocal or multicentric disease, and residual tumours after NC. Flattening of the contrast uptake time-intensity curve after the first chemotherapy cycle and complete absence of contrast uptake after the fourth cycle are observed in the responders. The patients with a concentric shrinkage pattern are good candidates for breast conserving surgery. H1 MR spectroscopy and nuclear imaging are very promising for identifying good responders early in the course of therapy (after one cycle). A low ratio of metabolic rate (18FDG-PET) relative to blood flow is a predictor of complete response. Nevertheless, all modalities are restricted in the imaging of very small residual tumour foci.

16 Proffered Paper Oral

Screening women with a familial or genetic predisposition to breast cancer: costs and effects of alternative screening policies

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Background: For the substantial proportion of women that have a more than average risk for breast cancer due to a familial or genetic predisposition, magnetic resonance imaging (MRI) is a promising screening tool. Estimates on breast cancer mortality reduction of screening these women are lacking, and randomized controlled trials are practically impossible.

Methods: In a prospective cohort study in 1952 women with increased breast cancer risk we estimated stage-specific sensitivity of different screening tests and resulting stage-shift by screen detection. Benefit of early detection was based on modeling estimates and pooled analyses of randomized mammography screening trials. We explored the effectiveness and cost-effectiveness of alternative screening policies for three cumulative lifetime (CLTR) risk categories: *BRCA1/2* mutation carriers (50–85% CLTR), a high-risk (30–50% CLTR) and a moderate-risk group (15–30% CLTR).

Results: Intensive surveillance including MRI in *BRCA1/2* mutation carriers is estimated to reduce breast cancer mortality by 50%, compared to 41% by mammography and clinical breast examination (CBE) only. Its effectiveness is almost twice as high compared to mammographic screening in women with population risk at 50. Screening *BRCA1/2* mutation carriers with biannual CBE and annual mammography and MRI from age 30 to 60 is at a cost of * 4314 per life-year gained (3% discounting). Offering MRI and mammography alternately at a 6 months interval is even more cost-effective. For the moderate-risk group, screening regimes with only mammography, alternating in combination with CBE, from age 40 to 50 years are most favorable in terms of cost-effectiveness (range * 3080–4764), and may lead to 25–31% breast cancer mortality reduction. Observed breast cancer incidence in the high-risk group did not differ substantially from the moderate-risk group. Waar zijn de low risks?

Conclusions: Addition of MRI in *BRCA1/2* mutation carrier surveillance is a very cost-effective screening policy, and should therefore be offered. For the moderate-risk category, intensive surveillance without MRI is defendable. Longer study follow-up is needed to advise a screening regime for the high-risk category.

Wednesday, 22 March 2006 14:15–16:00

SCIENTIFIC SESSION

How should we do phase II/III trials in the age of molecular biology?

17 Invited

When is a biological marker (or multimarker) ready to be tested in a clinical trial?

P.E. Lønning. *Haukeland University Hospital, Dept. of Medicine, Bergen, Norway*

Implementation of molecular biological parameters to test for therapy sensitivity may influence the way we are conducting clinical studies. So far the problem has been our limited knowledge about the mechanism controlling drug sensitivity in vivo. At this moment, only 2 predictive factors are used for therapy selection in breast cancer (BC); the estrogen receptor alpha (ER), and HER-2 amplification. Notably, these markers are also associated with breast cancer classification based on gene profiling in general [1], suggesting they both have a critical importance controlling tumor growth and behavior.

Yet while lack of ER and HER-2 expression signals non-responsiveness to hormonal manipulation and trastuzumab therapy respectively, patients expressing these parameters may still relapse despite optimal therapy, suggesting additional mechanisms of resistance to be involved. Considering chemoresistance in general, different attempts, including use of microarray techniques, have revealed gene profiles correlating to but not predictive of therapy responsiveness [2]. Considering individual markers, mutations in the TP53 gene as well as HER-2 amplifications have been associated with response to chemotoxics; however, none of these factors have revealed a sensitivity and predictivity sufficient for clinical implementations.

Clearly, there is a need for better predictive factors. The way forward probably lies in phase II neoadjuvant studies, in which proper tissue collection are made upfront and responsiveness to therapy carefully classified. There is actually little need to upfront hypothesize about individual predictive factors or array gene profiles predicting responsiveness. Assuming a time interval between editing a protocol and completion of patient data may last 3–5 years; most likely there will be a panel of novel potential predictive factors identified within that time interval. In this way, different phase II trials may identify and cross-validate the predictive value of individual as well as gene profile markers. Assuming resistance may be due not due disturbances in individual factors but rather disturbances in "functional pathways" [3], identification of certain markers may suggest other parameters involved up-/down-stream in the same pathways should be studied as well.

When is a parameter ready to be evaluated in a phase III study, selecting patients for individual therapy based on molecular profiling? This should mean some patients would be allocated to an experimental arm based on molecular testing and, as such, allocated away from standard therapy. In an ethical perspective however this is a decision not different from the ones we have been taking with respect to designing phase III trials in general; recent examples in breast cancer include trials evaluating aromatase inhibitors for adjuvant therapy. Thus, as soon we have sufficient evidence from phase II studies indicating expression of a particular marker may signal an experimental treatment approach to be advantageous, its clinical use should be confirmed in the phase III setting.

References

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18 Invited

Surrogate end-points: thick or thin ice?

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There is a long history of using surrogates in breast cancer research. For decades disease-free survival has been used as a surrogate for overall survival in studies assessing the efficacy of adjuvant treatment modalities