

INTRODUCTION

The IES is an inter co-operative group, randomized, double-blind, phase 3 trial in postmenopausal women with early breast cancer. Patients disease-free after 2-3 yrs tamoxifen were randomised to continue tamoxifen or switch to exemestane for a further 2-3 yrs to complete 5 yrs adjuvant endocrine therapy.

Bone mineral loss leading to osteoporosis and subsequent fractures is an important health problem in postmenopausal women. Whilst it is well known that tamoxifen preserves bone mass in post-menopausal women through its partial oestrogen agonist activity, there are concerns related to adverse effects on bone resulting from profound suppression of estrogen by aromatase inhibitors (AIs), such as exemestane, in women already at risk for the development of osteoporosis. The effects on bone of switching to an anti-aromatase agent such as exemestane, in patients pre-treated with tamoxifen, are not known.

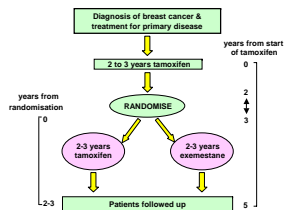
The IES study, which reported earlier this year (NEJM 2004; 350: 1081-92), provides an ideal opportunity to evaluate this. Part of the rationale for the design of IES was for patients to receive tamoxifen with its known protective effects on bone prior to switching to AI treatment with associated estrogen depletion.

Preliminary one year results of the IES Bone Sub-protocol, in which a subgroup of patients underwent detailed bone mineral density (BMD) and bone marker assessments, are reported.

IES STUDY DESIGN

4740 patients with ER positive/unknown, histologically or cytologically confirmed, completely resected, adequately treated unilateral adenocarcinoma of the breast & who had received 2-3 years of tamoxifen were randomized.

Figure 1: Study Design



STUDY DESIGN – BONE SUB PROTOCOL

206 patients were randomised into the bone sub-protocol.

Patients were eligible if they met the following criteria:

- lumbar spine & total hip BMD not osteoporotic (T scores below -2.5 standard deviations)
- no bisphosphonate therapy within previous 6 mths
- not used SERMs, HRT or calcium supplements for >1 mth in previous 6 mths
- no osteoporotic fractures & no bone fractures in previous 6 mths
- accurate BMD measurements through dual energy x-ray absorptiometry technically possible

END POINTS

Primary Endpoint:

- To assess & quantify the annual changes from baseline in lumbar spine and total hip BMD between patients who remain on tamoxifen and those who switched to exemestane during the entire study period.

Secondary Endpoints:

- to compare BMD between the two treatment groups at 12 mths and 24 mths post treatment randomization
- to compare changes in biochemical markers of bone turnover between the two treatment groups at each timepoint
- to assess the relationship between changes in biochemical markers of bone metabolism and changes in BMD
- to assess the changes in BMD over the 2 yrs after completion of study treatment
- to assess any effect on fracture incidence between the treatment groups during this study period

METHODS

- BMD was assessed by dual energy x-ray absorptiometry (DXA) of lumbar spine, total hip, femoral neck & Ward's triangle
- BMD was to be assessed at baseline and at 6, 12 & 24 mths and annually for 2 yrs following completion of treatment
- BMD measurements were forwarded to a Central Evaluation Facility (CEF) at Imperial College, London for analysis
- Data on spinal fracture incidence (thoracic & lumbar radiographs) and bone metabolism (biochemical markers of bone formation & breakdown) will be reported separately

STATISTICAL CONSIDERATIONS

Sample size: A total of 200 subjects (allowing for attrition) was required to detect a 2% difference in BMD, (SD of 4%) with 90% power and a 2-sided significance level of 0.05.

Statistical methods: BMD changes were expressed as percent changes from baseline and compared using two-sample (between treatment groups) and paired (within groups) t-tests. Absolute changes in T scores were also considered. All analyses used a 5% significance level & were performed by intention to treat.

PATIENT POPULATION

Study population: Between April 2000 and February 2003, 206 patients (100 exemestane; 106 tamoxifen) were entered into the IES bone sub-protocol from 17 centers.

Analysis population: Results are presented for lumbar spine and total hip DXA assessments performed within windows of +/- 1 mth of 6 & 12 mth follow-up visits. Analyses were conducted on a snapshot of data comprising data received by the CEF to 5th August 2004. This included 168 6 mth and 162 12 mth assessments.

RESULTS – BASELINE CHARACTERISTICS

The randomized groups were well balanced in terms of demographics and adjuvant/hormonal treatment received prior to randomization (table 1). At baseline, there were no significant differences in BMD, T score or proportion of osteoporotic patients between the two randomised groups (table 2).

Table 1: Demographic and Baseline Characteristics

	Exemestane N=100	Tamoxifen N=106
Age (years) - mean (SD)	61.3 (7.6)	59.9 (8.2)
Yrs since last menses - median (range)	10.5 (2 to 40.5)	8.5 (1 to 31.5)
Body mass index (kg/m ²) - mean (SD)	28.9 (5.2)	28.6 (5.8)
Prior chemotherapy - n (%)	37 (37)	42 (40)
Prior HRT - n (%)	29 (29)	41 (39)
Duration (months) initial tamoxifen treatment - median (range)	30.1 (24.0 to 36.9)	28.5 (24.1 to 37.5)

Table 2: BMD at Baseline

	Exemestane N=100	Tamoxifen N=106
BMD - mean (g/cm³) (SD)		
Lumbar spine	1.063 (0.157)	1.080 (0.151)
Total hip	0.965 (0.124)	0.976 (0.124)
T score - mean (SD)		
Lumbar spine	-0.56 (1.14)	-0.45 (1.12)
Total hip	-0.20 (1.00)	-0.12 (1.01)
Osteoporotic* - n, (%)		
Lumbar spine	42 (42)	36 (34)
Total hip	22 (22)	22 (21)
Either site	49 (49)	45 (42)

* T score between -2.5 & -1 (i.e. 1 to 2.5 SDs below mean) [WHO criteria]

RESULTS – CHANGES IN BMD

Percent change in BMD from baseline is shown in Figs. 2 (lumbar spine) & 3 (total hip). The difference in mean change at 12 months between randomized groups was estimated as 2.97% (95% CI: 1.94 to 4.00), p<0.0001 for lumbar spine & 1.57% (0.81 to 2.33), p=0.0001 for total hip. Changes from baseline were also greater in the exemestane arm at the femoral neck (12 mths: p=0.0003) & Ward's triangle (12 mths: p=0.052).

Figure 2: Percent change in lumbar spine BMD

Graph shows mean and 95% CI

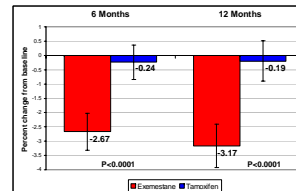
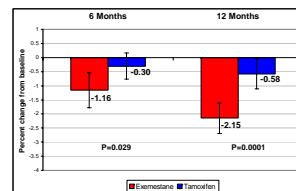


Figure 3: Percent change in total hip BMD

Graph shows mean and 95% CI



A similar pattern was seen when considering changes in T score (table 3). Four patients became osteoporotic (T score -2.5 or less) at the lumbar spine or total hip during the 1st yr of follow-up. All received exemestane & were osteoporotic at baseline.

Fracture Incidence:

In the IES main study, more patients reported fractures in the exemestane group (91) than the tamoxifen group (68) but this difference was not statistically significant (p=0.06). Of these, 20 in the exemestane group & 14 in the tamoxifen group were osteoporotic (p=0.30).

Table 3: T-scores

	Exemestane		Tamoxifen	
	6 months	12 months	6 months	12 months
Lumbar spine - n	77	77	80	85
Mean T score (SD)	-0.98 (1.12)	-0.86 (1.23)	-0.51 (1.21)	-0.49 (1.18)
Change from baseline				
Mean	-0.23	-0.27	-0.02	-0.02
(95% CI)	-0.29 to -0.17	-0.34 to -0.20	-0.07 to +0.03	-0.09 to +0.04
Total hip - n	78	77	80	84
Mean (SD)	-0.42 (0.94)	-0.41 (0.94)	-0.14 (1.00)	-0.23 (1.00)
Change from baseline				
Mean	-0.09	-0.16	-0.02	-0.05
(95% CI)	-0.14 to -0.04	-0.21 to -0.12	-0.06 to +0.02	-0.09 to -0.01

CONCLUSIONS

- Tamoxifen protection was lost rapidly – differences in BMD appear within six months of stopping treatment with tamoxifen and commencing with exemestane
- The observed decrease in BMD at 6 months could be due to the dual effects of tamoxifen withdrawal and treatment with exemestane
- BMD loss in patients who switched to exemestane was similar to that seen with other AIs at 2-3% in the first year of therapy
- 2 yr data will provide information on whether the rate of BMD change in the exemestane arm is less once the confounding effect of tamoxifen withdrawal has passed.
- Estimated 4-5% loss over 2-3 yrs would be consistent with a fall in T score of around 0.5 & a 50% increase in fracture rate
- Post-treatment follow-up will assess recovery of BMD after cessation of therapy

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