499 Poster

Prospective assessment of clinical rheumatologic features and magnetic resonance imaging (MRI) changes in the aromatase inhibitor (AI)-associated arthralgia syndrome

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Background: AI-associated arthralgia/musculoskeletal pain affects a large proportion of patients, adversely affects quality of life and limits compliance to the potentially curative anti-hormonal treatment of hormone sensitive breast cancer. AI-associated arthralgia syndrome predominantly affects the hands but its exact mechanism remains unclear. Our purpose was to investigate the changes in clinical rheumatologic features and MRI of hands and wrists in AI- and tamoxifen-users.

Patients and Methods: This is a prospective single-centre study including consecutive postmenopausal patients with early breast cancer receiving either tamoxifen or an AI. At baseline and after 6 months, patients filled in a rheumatologic history questionnaire and a rheumatologic examination including a grip strength test was done. At the same time points, MRI of both hands and wrists was performed. The primary endpoint was tenosynovial changes from baseline on MRI. Secondary endpoints were changes from baseline for morning stiffness, grip strength and intra-articular fluid on MRI. Wilcoxon signed ranks was used to test changes from baseline and the Spearman correlation coefficient to assess the association between rheumatologic and MRI changes from baseline.

Results: Of 35 patients included, 17 completed all the planned investigations at the time of this analysis and are included in this report (12 patients on AI, 5 on tamoxifen). Mean age was 65 years and patients were on average 14 years past menopause. At 6 months, patients on AI had a decrease in grip strength ($p = 0.0049$) and an increase in tenosynovial changes ($p = 0.0010$). The decrease in grip strength correlated well with the tenosynovial changes on MRI ($p = 0.0074$). Only minor changes were seen in patients on tamoxifen. AI-users reported worsening of morning stiffness and showed an increase in intra-articular fluid on MRI. Two patients on an AI discontinued treatment early prior to the re-evaluation at 6 months due to severe arthralgia.

Conclusions: The functional impairment of hands in the AI-associated arthralgia syndrome is characterized by tenosynovial changes on MRI correlating with a significant decrease in hand grip strength. The excellent correlation between clinical and MRI findings provides an objective substrate for the subjective complaints of the AI-associated arthralgia syndrome. The data on the total 35 patients will be available at the time of the meeting and an updated analysis will be presented.

500 Poster

Effects of adjuvant aromatase inhibitors on bone mineral density – observations from clinical practice

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Background: Aromatase inhibitors (AI) play an important role in the treatment of postmenopausal (PM) women with hormone receptor positive (HR+) early breast cancer (EBC). Information is sparse on the long-term toxicities of adjuvant AI therapy (tx), outside of a clinical trial setting. This study reports on the effects of AI tx on Bone Mineral Density (BMD) changes, over time, in patients (pts) with EBC.

Methods: PM women with HR+ EBC who were treated with an AI at our centre between Jan 1/99 and Dec 31/06 were included in this analysis. Data was retrospectively collected and included: demographics, comorbidities, duration of AI tx and toxicities including BMD changes.

Results: 640 pts were identified for this analysis. Average age was 60.3 yrs (range 29.3−91.6) with the majority of pts having stage I (31.7%) or II (54.4%) disease. Median duration of AI tx was 3.4 yrs (range 0−5.7); average overall hormonal tx (AI + Tamoxifen (TAM)) was 4.1 yrs (range 0.1−14). TAM was used in 380 pts (59.3%). A total of 528 pts in this analysis (82.5%) had at least one BMD performed; 218 pts had a single BMD (41.3%); 177 pts (33.5%) had two; 94 pts (17.8%) had three and the remainder (39, 7.4%) had four or more BMD's. The majority of pts (298, 56.4%) did not have a pre-AI BMD and only 9 pts had their BMD pre-TAM tx. Average time between BMD tests was 18 mo (range 1–125.8). Interval changes within pts in BMD T-scores averaged −0.16 (range −2.54 to +2.10) in the hip and −0.21 (range −2.15 to +2.53) in the spine. Osteopenia was reported in 24 and 53 pts (hip and spine respectively); osteoporosis was only reported in one case each. Bisphosphonates were used in 39.4% of pts; calcium and VitD tx was frequently used (63.8% and 59.1% respectively). Fractures occurred in 4.2% of pts with 0.9% in the hip/spine and 0.9% in the wrist.

Conclusion: Major Adjuvant trials with AI's (ATAC, BIG 1-98, IES) have clearly demonstrated the detrimental impact of AI tx on BMD. In this study, with a median duration of AI tx of 3.4 years, most of women had a least one BMD measurement (33.5% had 2) in keeping with current ASCO surveillance recommendations. There was, on average, a relatively small decrease in BMD scores and only one new case of osteoporosis over the period of observation. Fractures were rarely seen. While AI tx has been shown to have a potential negative impact on BMD this was not observed in our clinical practice. Ongoing followup is needed.

501 Poster

Internal mammary arteries develop a thicker neo-intima following irradiation for breast cancer

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Background: Epidemiological studies have shown that vascular damage is an important determinant of late radiation morbidity and mortality in breast cancer patients, thus reducing the therapeutic benefit of radiotherapy. It can also be a cause of graft failure after reconstructive surgery. This study was designed to evaluate the pathogolgical changes occurring in medium-sized arteries following radiotherapy.

Patients and Methods: 5 mm biopsies from the internal mammary artery (IMA) used for the anastomosis in breast reconstructive surgery were obtained from 19 breast cancer patients irradiated to the internal mammary chain and from 25 patients without prior radiotherapy. Arterial biopsies from the deep inferior epigastric perforator (D.I.E.P.) flap used for the reconstruction were used as an internal control. Clinical and treatment parameters were recorded. Measurements were made on histological sections of paraffin embedded arteries. Using imaging analysis software we determined the degree of neo-intimal thickening by calculating the ratio of the thickness of the intima to the thickness of the media (intima-media thickness, IMT). The proteoglycan content of the media was measured by quantifying the level of Alcian Blue staining and collagen content was determined using Sirius Red staining.

Results: In the control and radiotherapy groups respectively, the mean ages were 47 ± 9 and 45 ± 8 years, and the mean body mass index $28 \pm 5\ kg/m^2$ and $26 \pm 5\ kg/m^2$. Few patients smoked, with a mean of 4 and 3 pack-years respectively. In the irradiated group the mean dose was 49 ± 3 Gy, the mean time since radiotherapy was 4 years (range 0.8−19 years). The IMT increased significantly from 1.7 to 2.5 ($p = 0.04$) in irradiated compared to unirradiated vessels when the measurements were corrected for the IMT of the D.I.E.P. artery. Further, we measured a significant increase in the mean interstitial proteoglycan content of the media from 59.9% to 69.8% ($p = 0.05$) in irradiated vessels. We observed no significant differences in the total collagen content in irradiated versus unirradiated vessels.

Conclusions: Significant proliferation/thickening of the neo-intima, considered a precursor of atherosclerotic plaque development, was seen in irradiated vessels compared to unirradiated. Further, radiation caused an increased interstitial proteoglycan content of the media. We are currently including more patients in the study and relating vessel changes to the graft outcome.