Endocrine Therapy

Guidance

Everyone who is ER+ offered adjuvant endocrine therapy. *(Perhaps we should be more selective as this therapy is poorly tolerated by patients and thus poor adherence at 1 year).*

ABS/NICE – guidance for extended therapy

- Peri/pre-menopausal = give tamoxifen 5yrs and consider 10yrs.
- If <35yrs or receiving chemo i.e they are high risk then discuss OFS and AI/tamox (see young patients cheat sheet)
- Post-menopausal = LN+ve/T2>- offer extended AI
- DCIS = 'consider' Endocrine Tx adjuvantly [in practice we never give it in DCIS]

Evidence - Tamoxifen, Aromatase inhibitor, extended therapy, OFS brief

Tamoxifen

Use of tamoxifen for 5 years was established in the late 80s: Both **NATO (1987)** and **NASBP-14** showed HR 0.8 with tamox v placebo in **node negative patients**. **NASBP-20** HR 0.78 when tamox was added to **chemo**. This was confirmed in the key meta-analysis **EBCTG 2011 Lancet Meta-analysis** (20 trials, 21+k patients). Considering the subset of patients with proven ER+ status (10k):

- **Recurrence rates ½ in first 5 years, ⅓ at 10 yrs** (RR 0·53 during years 0–4, and RR 0·68 during years 5–9; but RR 0·97 during years 10–14) but no further gain after 10 yrs.
- Breast cancer **mortality** was reduced by about **30% the first 15 years** (RR 0·71 during years 0–4, 0·66 during years 5–9, and 0·68 during years 10–14).
- This was independent of progesterone receptor status, age, nodal status, or use of chemotherapy.
- Approx 80% compliance.

Justifying use AI in post-menopausal woman:

ATAC (Arimidex, Tamoxifen, Alone or in Combination) ~40K patients, 10yrs FU. Combination arm discontinued. This was the main trial that showed that AI is superior to Tamoxifen. Recurrence Rates at 5 and 10 years were 9.8% vs 12.5% and 19.7% vs 24% with tamoxifen vs AI respectively. Interestingly this trial preceded everyone being tested for ER status so reported as a sub-group. DFS at 10 years with AI vs tamox = HR 0.91 in all and HR 0.86 in ER+ subgroup. **Reports absolute benefit of AI over tamoxifen of 2.7% and 4.3% at 5 and 10 years**. Access at: https://doi.org/10.1016/S1470-2045(10)70257-6

BIG 1-98 = 8k patients randomised to letrozole, tamoxifen or switch. **DFS 2.9% absolute benefit.** OS equal.

Endocrine therapy.

Originally collated by Miss Amy Robinson. Last updated: May 2023

EBCTG 2015 meta-analysis on 30k pts, 4 arms: Tamox alone, AI alone or switch at 2-3yrs. It showed that AI superior to Tamox: Breast cancer mortality 12.1% v 14.2 % tamox and AI respectively ie a **2.1% ARR in breast cancer death.**

Crucially it is while on treatment - AI reduces recurrence rates by 30% (proportionately) compared with tamoxifen while on, but not after stopping. 5 years AI reduces 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen, hence by about 40% (proportionately) compared with no treatment.

Extended therapy

Then **ATLAS** and **aTTom** showed benefits of extended tamox to 10 yrs - **Absolute benefit of 2.8% (NNT 57-quite high given the side effect profile) in OS** when given for 10 years. Patients should be aware that there is a doubling of Endometrial Ca (3.1% v 1.6% in 5 yrs), Mortality (0.4%) and PE (0.64%). Unfortunately, no good evidence for post-menopausal women - **MA-17** of 5k women switched women after 5 years of tamox to AI or nothing OS HR 0.61 if node +ve, hence guidance. Have to take into consideration toxicity/tolerance. **NASBP-42** showed reduced risk of second cancer. *To date no trials have proven the survival benefit of AI for 10 years.*

Ovarian Suppression

The use of OFS is summarised in the young patients cheat sheet but these trials are fraught with difficulties - see Grant Harris's excellent presentation in the literature club section. Need to be aware that the main benefit will be in woman whom are high risk - will go onto receive chemotherapy AND remain pre-menopausal post chemo. The best benefit is disease free rather than overall survival. *Be aware of applying this to the HER2+ve cohort as only 60% of HER2+ cancers received anti-HER2 treatment and this area has moved very quickly -see HER2 disease cheat sheet!

Meta-analysis of the two main trials by **Pagani et al (of TEXT and SOFT)** shows **DFS**:

- Tamox alone = 67.7%
- Tamox + OFS = 78.7%
- Exemet + OFS = 83.4% hence guidance that if <35 this should be discussed.

There is small survival benefit with addition of OFS to tamoxifen in 2018 update

As prophylaxis in HIGH-RISK patients?

IBIS 1 - Tamoxifen in high risk patients = only works to prevent ER+ cancers (about ½), hence only recommended in BRCA 2 not 1. IBIS-2 was post-menopausal women and AI, same as IBIS1.

IBIS 2 - Also looks, AI as risk reduction

**Note: In women who develop amenorrhoea on chemo MUST WAIT 2 YEARS to establish as may resolve. STOP TAMOX 8/52 then 2x blood samples 6/52 apart showing FSH>30.