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Update on optimal duration of adjuvant antihormonal therapy

Caveats with this document:

Based on consensus practice where there is absence of evidence
Needs consensus with oncology colleagues
Decision on initial endocrine therapy is between clinician and patient.

Introduction

Evidence is accumulating that OS and DFS is improved with extended duration of antihormonal therapy. In the absence of definitive evidence and considering the principles of MA 17, ATLAS & ATTOM consider extended endocrine therapy for a further 5 years after considering patient preference, relapse risk and co-morbidities.

Patients who have completed 5 years of tamoxifen therapy

Premenopausal women: Offer further tamoxifen for a total antihormonal duration of 10 years to assist in both relapse prevention and chemoprevention.

Post menopausal: Offer tamoxifen for 10 years or switch to AI for 5 years.

Definition of menopause
CAUTION: Blood tests/ FSH analysis can be unreliable during peri menopause and while on tamoxifen. If in doubt continue tamoxifen.

Post menopausal or prior ovarian suppression who have completed 5 years of AI

Reasonable options:

- Stop
- Continue AI to 10 years
- Switch to tamoxifen for a further 5 years

Implementation

It is the responsibility of breast teams to trigger a review of endocrine treatment at 5 years from diagnosis if they adopt a policy of extending the duration of antihormonal therapy.

For patients who are discharged from active hospital follow up at the breast unit, inform GP practice of any change in policy. GP practices are able to identify all patients on endocrine therapy and can review the prescription or rerefer to the breast unit for advice.

Patients who have stopped endocrine therapy for more than 12 months need not be included in recall.

Note:

Since this issue was initially discussed at the Working Group ASCO have published Burstein H, Temin S, Anderson H et al. *Adjuvant Endocrine Therapy for Women with Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update.* J Clin Oncol 2014; 32: 2255 - 2269. The group agrees broadly with ASCO's recommendations.

Background Literature Summary

The receipt of adjuvant endocrine treatment reduces recurrence and breast cancer specific mortality rates in women with ER/PR positive early breast cancer. The most recent EBCTCG overview showed a 30% reduction in breast cancer mortality throughout the first 15 years following 5 years of adjuvant treatment with tamoxifen.(RR=0.71for yrs 0-4 and 0.66 for yrs 5-9). The proportional reduction in risk of relapse for all time periods was 39% (RR=0.53 for yrs 0-4 and 0.68 for yrs 5-9). This benefit was independent of patient and tumour characteristics.

Tamoxifen and aromatase inhibitors are the current principle antihormonal therapies used as adjuvant treatment in women with ER+ early breast cancer.

Duration of endocrine therapy

Duration of Tamoxifen:
Breast cancer, especially ER+ positive disease is well recognised to have a long natural history with a 2% annual rate of relapse up to 15 years following diagnosis. Therefore, the challenge has been to determine the optimal duration of adjuvant endocrine treatment. The 1980's Swedish trial which compared 5 years to 2 years of tamoxifen showed that 5 years was superior in terms of EFS(RR=0.82) and OS(RR=0.82) . Overall survival at a median follow up of 5.5 years was 80% vs 74%. This result was confirmed by the CRUK trial

The NSABP B-14 extension study was the first large trial to assess the benefit of continuing tamoxifen beyond 5 years in the adjuvant setting. 1152 ER positive patients who had completed 5 years of tamoxifen were randomised between a further 5 years of tamoxifen or placebo. The trial was closed prematurely as the first interim analyses showed no benefit with longer duration of treatment. In fact, there was a reverse trend. The DFS @ 4years was 92% in the 5 year arm compared to 86% in the 10 year arm. This adverse effect with longer treatment was attributed to the potential reversed action of tamoxifen which occur with longer term use.

Following the NSABP B-14, 5 years of tamoxifen was established as a standard treatment in the adjuvant setting. However, it was increasingly recognised that 5 years of endocrine treatment had a long carry over benefit and to analyse if there was any extra gain from extended treatment the follow up period would have to be considerably longer than that in traditional trials. The NSABP B-14 was criticised for small numbers and premature termination resulting in short follow up duration.

ATLAS and aTTOM trials were started in the 1990s to re-examine the question.

ATLAS Trial: A very large trial which recruited 12,894 patients who had completed 5 years of tamoxifen randomised to a further 5 years or placebo. 53% were node negative and 53% had T size< 2cms. There was no grade analysis. Compliance after 2 years of randomisation was 84% in the treatment arm and 90% in the placebo arm. The 6,846 patients with ER+ disease were analysed for RFS and breast cancer specific survival, but all patients were analysed for side effects.

In ER+ women allocated to extended treatment there was a further reduction in risk of relapse(p=0.002), breast cancer specific mortality(p=0.01) and all cause mortality. This difference became apparent after 10 years following diagnosis. Out to year 10 RR for recurrence was 0.75, an absolute difference of 3.7% and RR for breast cancer mortality was 0.7, an absolute difference of 2.8%. This benefit was independent of patient age, menopausal status, tumour size or nodal status.

The aTTom trial in the UK had a similar design and recruited 6,539 women with ER+ or unknown EBC. The risk ratio (RR) for recurrence was 0.85 with an absolute reduction of 4% with longer treatment. There was a 2% reduction in mortality(RR=0.88) and these benefits were time dependent becoming apparent 7-10 years after diagnosis. These results from ATLAS and aTTOM along with results from trials of 5 years of tamoxifen SUGGEST 50% reduction in the risk of mortality with 10 years of tamoxifen compared to no treatment.

Clearly, in both trials the extended treatment arm was associated with increased morbidity. There was increased risk of PE(RR=1.87) and endometrial carcinoma (RR=1.74) but the mortality was not significantly different.

Role of Ovarian Ablation/ Supression in Pre-Menopausal Women:

The 1995 EBCTCG meta analysis of the ovarian ablation trials started prior to 1980 showed that in women below the age of 50, ablation of functioning ovaries by irradiation or surgery reduced the risk of relapse and improved survival when used as a sole treatment. Addition of ablation to cytotoxic chemotherapy was much less useful. Since then, several randomised trials have further assessed the role of ovarian suppression in the adjuvant setting in pre-menopausal ER+ breast cancer.

The ZEBRA trial was a large randomised trial that directly compared ovarian suppression to CMF chemotherapy and found the two treatments to be equivalent. This led to the conclusion that OS could be used as a reasonable alternative to cytotoxic chemotherapy. Since then chemotherapy has changed to second and third generation regimens which include anthracyclines and taxanes and this result is therefore, of less relevance to current practice.

Four main trials namely INT0101, ABCSG-VII, IBCSG11-93 and Zipp explored the role of OS in combination with cytotoxic chemotherapy. All failed to show a significant advantage with this strategy. There may be an advantage in combining tamoxifen with OS in younger women who remain pre-menopausal even after chemotherapy. The SOFT trial has reported on this question. At ASCO 2014, a joint analysis of the TEXT and exemestane arm of the SOFT trials was presented. OS+ Exemestane significantly reduced the risk of recurrence compared to OS+Tamoxifen . This is not practice changing. OS is not yet standard treatment in the adjuvant setting.

Aromatase Inhibitors (AI):

<u>Upfront or early switch</u>: Third generation AIs such as anastrazole, letrozole and exemestane are powerful alternatives to tamoxifen in postmenopausal women with ER+ breast cancer.

A recent meta analysis of all the adjuvant AI trials published by Dowsett et al concluded that AI used either as initial treatment or following 2-3 years of tamoxifen resulted in a significant

reduction in risk of recurrence and a non -significant reduction in mortality. At a median follow up of 5.8 years, the absolute decrease in recurrence rates with 5 years of AI compared to 5 years of tamoxifen was 2.9%(9.6%vs12.6%) with a non significant 1.1% decrease in breast cancer mortality. The switch strategy resulted in a recurrence rate difference of 3.1% (5.0%vs8.1%) at a mean of 3.9 years of follow up. The absolute decrease in breast cancer specific mortality was 0.7%

A recent 10 year update of the ATAC trial which compared 5 years of tamoxifen to 5 years of anastrazole showed a relapse rate difference of 2.7% at 5 years and 4.3% at ten years in favour of the AI group. There was no significant improvement in overall survival despite a decrease in breast cancer specific mortality. There are some as yet poorly defined concerns regarding a potential increased risk of cardiovascular events with anastrazole.

AI after 5 years of Tamoxifen: The seminal trial that explored this question was the NCIC-CTG MA.17 trial. 5,187 patients with ER+ breast cancer who had completed 5 years of adjuvant tamoxifen were randomised between placebo or 5 years of letrozole. All were postmenopausal at randomisation. At 4 years, there was an absolute difference of 4.6% in DFS in favour of extended treatment with letrozole. The statistically significant decrease in DFS and DDFS in the letrozole arm remains present even at 64/12 follow up with adjustments made for crossover(HR=0.52 for DFS& 0.61 for OS). These benefits were seen regardless of the menopausal status of the patient at the time of diagnosis. There have been smaller trials which have investigated the same question with similar conclusions.

However, hot flashes, arthralgia, myalgia were more common in the AI arm resulting in a compromise in QOL. There was also an increased risk of osteoporosis (5.8%vs 4.5%) .

Unanswered Questions:

Duration of AI therapy:

The majority of postmenopausal patients are on an AI from the commencement of antihormonal therapy. At present there is no level-I evidence to support the use of AI beyond a duration of 5 years. Phase III data is awaited. In the meanwhile, based on the evidence to date, it may be reasonable to continue AI beyond the standard 5 years in a higher risk postmenopausal woman, In the absence of toxicity data this needs careful discussion with the patient.

5 years of additional tamoxifen or switch to AI:

There is no head to head randomised trial to answer this question. The HR for overall survival (OS) in MA.17 at 64/12 follow up is 0.61(0.52-0.71) and in the combined ATLAS/aTTOM trials the HR for OS is 0.91(0.84-0.97). This suggests that a switch to AI following 5 years of tamoxifen may be more beneficial. In the absence of direct comparisons, this data should be interpreted with caution and should not be used as the only evidence to make treatment decisions.

Selection of women for switching from tamoxifen to AI:

As most of the patients who are post menopausal at diagnosis are initially commenced on an AI, the question of switch is essentially for women who are pre/peri menopausal at diagnosis and become postmenopausal during adjuvant treatment on tamoxifen. Determining menopausal status in this group can be complex as the standard parameters used to define menopause are often inaccurate. In the MA.17 trial, patients who were pre-menopausal at

diagnosis were regarded as having gone through menopause if they remained amenorrheic for 1 year or more with FSH/LH/serum estradiol levels in the postmenopausal range, Using these criteria only 5/5187 resumed regular menses on AI

Who needs extended endocrine treatment:

All the extended endocrine trials show that the majority of patients remain relapse free after 5 years of endocrine treatment resulting in small gains from extended treatment. None of the studies were able to identify any clinical or molecular marker that predicts for response to extended treatment. It is likely that patients who are at higher risk of relapse as identified by standard clinico-pathological criteria will have a higher absolute benefit from treatment but this is by no means certain. Standard prognostic tools such as NPI and 'adjuvant on line ' are helpful, but deciding on the optimal cut off timepoint so that treatment is both clinical and cost effective is a challenge.

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On behalf of the ABS Council

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Note:
Members of ABS Council and Committees met and discussed a set of topics on which it was felt clinical guidance was sought by ABS members. This document represents the considered, agreed opinions of experienced breast surgeons. It is not meant to supplant authoritative guidelines. Discussion and correspondence would be gratefully received by the ABS to lucydavies@absgbi.org.uk