Extended Endocrine Therapy in Early Breast Cancer – how long and who for?

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Abstract

Endocrine therapy for breast cancer is in a state of flux with much uncertainty about choice of agents and duration of therapy. The standard treatment span of 5 years usually incorporates an aromatase inhibitor in the majority of post-menopausal patients. Hormonal therapy has a cytostatic action that provides a biological rationale for continuing treatment for more prolonged periods to reduce risk of late recurrence in oestrogen receptor positive disease. Several trials of extended endocrine therapy for periods varying from 7.5 to 10 years have shown mixed results for gains in disease-free survival. The challenge is to assimilate available data and apply clinical judgment to tailor therapies taking account of intrinsic risk of disease recurrence, patient preference, tolerability to date and co-morbidities.

Introduction

Over the past two decades hormonal therapy for early stage breast cancer has become increasingly complex and no longer are patients offered the ubiquitous 5 years of tamoxifen therapy with or without ovarian suppression for pre-menopausal women. With the advent of aromatase inhibitors, there is now uncertainty about the optimum schedule for adjuvant systemic hormonal therapy in terms of choice of agent and duration of usage[1]. Risk stratification is being used to determine type of hormonal agent and whether patients should receive a standard course of 5 years total duration or 'extended' endocrine therapy up to 10 years. It should be noted that there is a significant risk of relapse for

many hormone receptor positive breast cancers with half of these cases occurring beyond 5 years and recurrence risk continuing to increase throughout the first 20 years of follow up. Indeed, the hazard plots for breast cancer death indicate that patients with oestrogen receptor (ER) negative tumours have greater risk of death from breast cancer than do patients with ER positive tumours during the initial 8 years following diagnosis[2]. However, after that 8 years period, the risk of breast cancer death is greater for patients with ER positive tumours when compared to those with ER negative tumours. Eight years following initial breast cancer diagnosis, the annual risk of breast cancer death for patients with ER positive tumours plateaus at about 1-2% per year. Thus, delayed recurrences are more concerning for patients with ER positive breast cancers than those with ER negative tumours [FIGURE 1]. There is a substantial risk of recurrence in absolute terms for smaller node negative tumours (T1N0) in years 15 to 20 after initial diagnosis of breast cancer. This justifies exploration of extended endocrine therapy as a clinical strategy.

Standard duration adjuvant endocrine therapy

1) *Tamoxifen* – a meta-analysis by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) involving 21,457 early breast cancer patients evaluated clinical trials comparing 5 years of tamoxifen usage versus placebo. These revealed profound effects of tamoxifen therapy upon both recurrence and mortality that was evident throughout the first 15 years of follow up. The absolute gains in recurrence were 11.8% and mortality 9.2% over this time period [2p<0.00001][3]. These data underpin prescription of 5 years of tamoxifen as standard adjuvant hormonal therapy for the majority patients prior to widespread incorporation of aromatase inhibitor therapy into adjuvant hormonal schedules[4,5].

2) *Aromatase inhibitors* – like many novel agents for treatment of breast cancer, aromatase inhibitors were initially used in the advanced disease setting where they offered advantages over tamoxifen and progestins as first- and second-line therapies respectively. In the adjuvant setting, aromatase inhibitors have generated an element of uncertainty in the optimum hormonal therapy for post-menopausal women with oestrogen

receptor positive tumours. A blanket policy is no longer appropriate and a selective strategy with tailored therapy based on risk of relapse is the preferred option. These agents have been explored as upfront therapy for 5 years or sequenced in an early 'switch' strategy after 2 – 3 years of tamoxifen[6-10]. Those patients at greatest risk of relapse may benefit most from an upfront aromatase inhibitor whilst those with lower hazard rates for relapse can be treated with an 'early switch' regimen involving tamoxifen for 2 – 3 years followed by an aromatase inhibitor for a total duration of 5 years. Benefits in terms of disease-free and overall survival must be balanced against longer term adverse effects on bone health and cognitive function as well as cost. Some patients at very low risk of relapse may derive minimal additional benefit from incorporation of an aromatase inhibitor into their treatment schedule and should receive tamoxifen only. Large randomized clinical trials such as BIG 1-98 have confirmed that 5 years of an aromatase inhibitor is better than tamoxifen for 5 years with gains in both recurrence and mortality[7,8]. Furthermore an aromatase inhibitor (2 – 3 years) sequenced after tamoxifen (2 – 3 years) is an alternative to 5 years of an aromatase inhibitor with a formal meta-analysis demonstrating lower rates of recurrence for aromatase inhibitor therapy (approximately 20% proportional reduction) and a small mortality gain. The overall survival benefit at 8 years was 1.7% in favour of aromatase inhibitors[11].

Extended duration adjuvant endocrine therapy

Although the benefits of breast cancer adjuvant systemic therapy were generally assumed to be constant (i.e. proportional) over time, an analysis of 19 adjuvant systemic therapy trials in the National Surgical Adjuvant Breast and Bowel Project (NSABP) database indicate that treatment benefits diminish significantly at specific time points following surgery[12]. This suggests that the benefits of adjuvant systemic therapy may often reduce after cessation of therapy, and provides a rationale for consideration of extended adjuvant therapy for some subsets of patients.

Trials of extended tamoxifen therapy

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial randomised patients after surgery to 5 years of tamoxifen or placebo, and showed a statistically significant disease-free survival (DFS) and overall survival (OS) benefit for tamoxifen. To address the question of optimum duration of therapy, patients in the NSABP B-14 study who were alive and disease-free after 5 years of tamoxifen were then again randomised to an additional 5 years of tamoxifen or placebo. In the NSABP B-14 trial, there was no overall benefit from more prolonged therapy in a group of node negative patients with early stage breast cancer. The risks associated with more prolonged therapy that include thromboembolism and endometrial carcinoma, were considered to outweigh any benefits and indeed a small decrease in disease-free survival was documented[13,14]. A similar comparison was undertaken in the larger ATLAS (Adjuvant Tamoxifen – Longer against Shorter) trial involving almost 7000 patients who had received the standard 5 years of adjuvant tamoxifen therapy were randomized to continue tamoxifen for a further 5 years or stop (control group)[15] [FIGURE 2]. In contrast to the NSABP B-14 study, this revealed a positive impact on mortality from longer duration of tamoxifen usage with statistically significantly fewer recurrences in the group receiving 10 years of tamoxifen therapy (rate ratio (RR) = 0.75) at a mean follow up of 7.1 women years. Interestingly, there was minimal effect of more prolonged treatment during years 5 - 9 (RR 0.90) with benefit and divergence of curves occurring mainly after year 10 (i.e. whilst not receiving active treatment). There was a significant reduction of breast cancer mortality with a rate ratio of 0.71 and an absolute reduction of 2.8%. These benefits were evident after year 10 of follow up and were additional to any 'carry over' effect that is evident during years 5 – 10 but has largely disappeared after 10 years. There was no excess of uterine cancer deaths in pre-menopausal women and for those over 50 years of age the incidence of uterine cancer was 2.6% versus 1.6% ($2p = 0.08$), representing a net loss from endometrial cancer of 0.2%. The smaller aTTom trial revealed a more modest effect on mortality from 10 years of tamoxifen at 15 years with a hazard ratio of only 0.85 [16].

Trials of extended therapy with tamoxifen and an aromatase inhibitor

The seminal MA.17 trial was the first to explore extended endocrine therapy involving administration of an aromatase inhibitor (letrozole) after completion of a standard 5 years of tamoxifen therapy. This sequence of extended endocrine therapy with a combination of tamoxifen and an aromatase inhibitor led to improved disease-free survival with a marked reduction in the hazard ratio [HR= 0.52]. Moreover, there was a significant survival advantage for node positive patients [HR = 0.61]. Of note, this schedule involving an aromatase inhibitor was effective for women who were initially pre-menopausal but subsequently become post-menopausal during the period of treatment[17,18].

The MA.17R trial randomized patients to either 5 years of letrozole or 5 years of placebo following an initial 5 years of treatment that included one of the following options [FIGURE 3][19]:

a) aromatase inhibitor for 5 years
b) early switch of tamoxifen (2-3 years) followed by an aromatase inhibitor (2-3 years)
c) receipt of more than 5 years treatment as per MA.17 protocol

At a median follow up of 6.3 years, trial results showed an increase in disease-free survival with an absolute benefit of 4% (letrozole arm = 95%; placebo = 91%). There was a relative decrease in risk of recurrent disease of 34% [HR 0.66; p = 0.01]. A noteworthy observation from this trial of extended endocrine therapy was an increase in bone fractures (14% versus 9%; p = 0.001) and more cases of new onset osteoporosis (11% versus 6%; p<0.001) for those randomized to receive additional endocrine therapy with letrozole[19].

Results of several other trials of extended hormonal therapy were reported concurrently at the San Antonio Breast Cancer Symposium (SABCS) in December 2016. Despite being eagerly anticipated, these trials were largely negative in terms of clinical outcomes and tempered enthusiasm for extended therapy in the immediate aftermath of these presentations. The DATA study compared 3 versus 6 years of anastrozole (1mg daily) following 2 – 3 years of tamoxifen therapy in hormone receptor positive early stage breast cancer[20]. The trial randomized 1912 post-menopausal women with oestrogen (ER)

and progesterone receptor (PR) positive breast cancer who remained disease-free after an initial treatment period of 2 – 3 years with tamoxifen. The number of women receiving 3 and 6 years of anastrozole was 823 and 827 respectively on an intention-to-treat basis. The primary outcome measure was adapted disease-free survival for any cancer event including invasive or non-invasive cancer recurrence (local, regional or distant), second non-breast primary cancers and death from any cause. Adapted referred to survival beyond 3 years after randomization as all patients received the same endocrine treatment for this initial time period. The secondary endpoint was overall survival. Analysis of results revealed no significant difference in adapted disease-free survival at 5 years between treatment groups (79.4% for 3 years versus 83.1% for 6 years [HR 0.79 (CI 0.62 – 1.02); p = 0.07]). Furthermore, there was no impact of more prolonged anastrozole therapy on overall survival [HR 0.91 (CI 0.65 – 1.29); p = 0.6]. Notwithstanding these negative outcomes for extended therapy, subgroup analysis revealed a significant improvement in adjusted disease-free survival for larger node positive tumours (ER/PR positive, HER2 negative) in receipt of chemotherapy [HR 0.58 (CI 0.39 – 0.89); p = 0.01]. Prolonged anastrozole therapy was associated with increased morbidity from a range of symptoms including arthralgia/myalgia (58% versus 53%), osteoporosis/osteopenia (21% versus 16%) and arterial thrombotic events. It was concluded that there was no net benefit from extended endocrine therapy for most patients with early stage breast cancer.

The IDEAL trial likewise randomized almost 2000 patients to receive either 2.5 year or 5 years of letrozole (2.5mg daily) following an initial 5 years treatment period involving several endocrine options[21]:

a) tamoxifen for 5 years
b) early switch of tamoxifen (2-3 years) followed by an aromatase inhibitor (2-3 years)
c) aromatase inhibitor for 5 years

Hence some patients within this trial could potentially be treated with up to 10 years of an aromatase inhibitor and this may have relevance to current treatment recommendations for type and duration of adjuvant endocrine therapy. The primary and secondary endpoints for this study were disease-free and overall survival respectively. A

comparison of results at a median follow up of 6.5 years failed to show any statistically significant differences for either trial endpoints or the metastasis-free interval. Thus hazard ratios for disease-free and overall survival were 0.96 (CI 0.76 – 1.20; p = 0.70) and 1.08 (CI 0.81 – 1.45; p = 0.59) respectively. In terms of side effects, this study reported a comparably high incidence of toxicity for both groups of 70% that included symptoms of arthralgia, myalgia, bone fracture and osteoporosis/osteopenia. In particular the authors attributed a low number of events to extended therapy and once again this has relevance to treatment guidelines. The equivalence of clinical outcomes within this trial led to the conclusion that there is no justification for extending aromatase inhibitor therapy beyond 2.5 years for the majority of patients (subgroup analysis did not identify any patients benefiting from 5 years of extended therapy). Thus a total of 7.5 years of sequential therapy with tamoxifen/aromatase inhibitor or aromatase inhibitor monotherapy is sufficient and should not be extended out to 10 years[21].

The NRG/NSABP B-42 study was the third in this trilogy of trials on extended endocrine therapy to be presented at the SABCS2016. This large trial randomized almost 4000 post-menopausal hormone receptor positive women to receive 5 years of letrozole or placebo after 5 years of endocrine therapy consisting of either an upfront aromatase inhibitor (5 years) or an early switch policy as for the DATA and IDEAL trials [FIGURE 4][22]. Patients were recruited between September 2006 and January 2010 with half being node positive and one-third of patients aged less than 60 years. At a median follow up of 6.9 years there was a reduction in the primary endpoint of disease-free survival in favour of letrozole but this was not deemed to be statistically significant due to adjustment of the pre-defined 2-sided p-value to 0.0418 from four interim analyses (alpha spending). As a consequence of this statistical quirk, the hazard ratio of 0.85 was no longer below the stipulated p-value for level of significance. There was no benefit for the secondary endpoint of overall survival (p= 0.22) but extended treatment with letrozole was associated with an improvement in the breast cancer-free interval [HR 0.71; p=0.003] – this included recurrence and contralateral disease. In addition, there was improvement in the cumulative incidence of distant recurrence [HR 0.72; p=0.03]. Although the reduction in disease-free survival is statistically non-significant in a formal sense, it might be argued that results of this

NSABP B-42 trial are concordant with those of MA.17R for which a clinically meaningful improvement in this primary endpoint was demonstrable. Interestingly, no increase in numbers of osteoporotic fractures attributable to extended endocrine therapy was found in the NSABP B42 trial. It has been pointed out by Mamounas that these two trials are 'more similar than different' and collectively supportive consideration of extended endocrine therapy for selected patients taking account of patient preference, relapse risk and co-morbidities[23].

Results of the Austrian Breast Cancer Study Group (ABCSG) -16 trial were presented the following year at SABCS. This randomized phase III trial likewise involved almost 4000 patients (n = 3,484) and compared 2 years with 5 years of extended endocrine therapy (anastrozole, 1mg daily)[24]. After a standard 5 years initial treatment (tamoxifen or an aromatase inhibitor alone or sequenced), patients were randomized to one of these treatment groups with the primary endpoint being disease-free survival. The latter was almost identical with a similar proportion of patients (22%) developing recurrence or relapse irrespective of treatment allocation (2 years (377/757) versus 5 years (380/757)). The fracture rate was noted to be higher in years 3 to 5 leading to the conclusion that 2 years of extended therapy with anastrozole is sufficient for most patients and more prolonged treatment should not be recommended on the basis these trial data.

Discussion

The results of the three aforementioned trials presented at SABCS2016 were a surprise to many and prompted a re-thinking of extended endocrine therapy for patients with early stage breast cancer. It is essential to balance any clinical benefit with potential side effects, patient wishes and costs. For these reasons, recommendations for extended endocrine therapy have become highly individualized and this is reflected in the looser language of formalized guidelines. There is an element of clinical uncertainty about how to use the current database to accurately and confidently select patients for more prolonged periods of endocrine therapy. Key factors to consider are higher disease stage, young age and patient preference together with adherence to prescribed medications. Biomarker information can potentially aid prediction of late recurrence and relevant

genomic classifiers with clinical utility include Oncotype-DX, PAM50, Endopredict and Breast Cancer Index[25]. Extended endocrine therapy should be considered for most pre- and post-menopausal hormone receptor positive women receiving chemotherapy as these are more likely to be at high risk of relapse based on conventional clinical and pathological factors. There are two broad groups of patient to consider in the context of extended endocrine therapy. Firstly, those patients that have already embarked on a 5 year course of adjuvant hormonal therapy and secondly those patients with newly diagnosed breast cancer and no prior exposure to tamoxifen or an aromatase inhibitor. Within each of these groups there are defined categories of patients – low risk, pre-menopausal, peri-menopausal and post-menopausal. A particular concern about extended therapy relates to women who have received an aromatase only as adjuvant therapy; extended therapy should be considered cautiously for this group with attention to tolerability to-date, relatively young age (long life expectancy), bone health and possession of a contralateral breast.

For those patients coming to the end of a 5 years treatment span involving an early switch from tamoxifen to an aromatase inhibitor, then a reasonable option is to continue with the aromatase inhibitor for a total duration of 7.5 years (this would be supported by data from the IDEAL and ABCSG-16 trials). For those in receipt of 5 years tamoxifen only as a consequence of being low risk, then further endocrine therapy is not indicated. These patients have already survived 5 years and have a very good prognosis by virtue of histology and stage. Extended therapy should not routinely be offered in these circumstances unless demanded by the patient themselves. For a small number of women, continued treatment can be a 'security blanket' and stopping can trigger much distress (despite informed discussion of risks and benefits). For patients in receipt of 5 years of an aromatase inhibitor, extension of therapy out to 7.5 – 10 years should be considered (taking account of previously mentioned factors). It should be noted that there is no evidence at the present time supporting 10 years of an aromatase inhibitor and the IDEAL trial showed no benefit for disease-free nor overall survival but potentially included patients with 10 years of an aromatase inhibitor (no separate subgroup analysis based on endocrine regime prior to randomization). Those women who are pre- or peri-menopausal

and *not* low risk should receive 10 years of tamoxifen therapy based on results of the ATLAS trial.

Several endocrine treatment options exist for newly diagnosed breast cancer patients with hormone receptor positive disease and no prior exposure to tamoxifen or an aromatase inhibitor. For post-menopausal low risk women, 5 years of an aromatase inhibitor should suffice with tamoxifen an appropriate alternative when contraindications to an aromatase inhibitor are apparent (e.g. history of osteoporosis or low bone mineral density score consistent with a degree of osteopenia). For all other post-menopausal women, 10 years of an aromatase inhibitor should be prescribed with the default option of tamoxifen if not tolerated or there is radiological evidence of poor bone health. On the basis of current trial data discussed above, another option is to start post-menopausal patients on tamoxifen for 2 – 3 years and then change to an aromatase for 5 – 7.5 years – this would provide between 7.5 and 10 years of endocrine treatment in total. Once again, this might be appropriate when bone health is questionable or there is mild osteopenia. For pre-menopausal women below the chemotherapy threshold, 5 or 10 years of tamoxifen is recommended whilst 10 years would nowadays be prescribed routinely for those above the chemotherapy threshold. It is advisable to treat peri-menopausal women at presentation the same as pre-menopausal as measurements of hormone levels (e.g. follicle stimulating hormone) during or immediately after chemotherapy can be problematic.

Conclusion

It is recognized that hormone receptor positive breast cancer has a long natural history characterized by a proclivity for chronic residual disease and late distant recurrence. Endocrine therapy acts upon cells in a cytostatic manner rather than killing cells and this is the rationale for prolonged therapy in order to maintain dormancy and suppress the process of 'kick-starting' foci of micrometastases. Nonetheless, trials to date of extended endocrine therapy have yielded modest results in terms of improving disease-free survival but highlighted disadvantages of more prolonged therapy in terms of side effects and costs. Once patients reach the 5 year time point from diagnosis, endocrine treatment options should be carefully reviewed taking account of several factors including intrinsic

risk of disease recurrence, patient preference, tolerance of endocrine therapies to date and co-morbidities. Current recommendations favour up to 10 years of an aromatase inhibitor for most post-menopausal women at moderate to high risk with 5 years treatment only with either tamoxifen or an aromatase inhibitor confined to low risk pre- and post-menopausal women respectively.

3672 words

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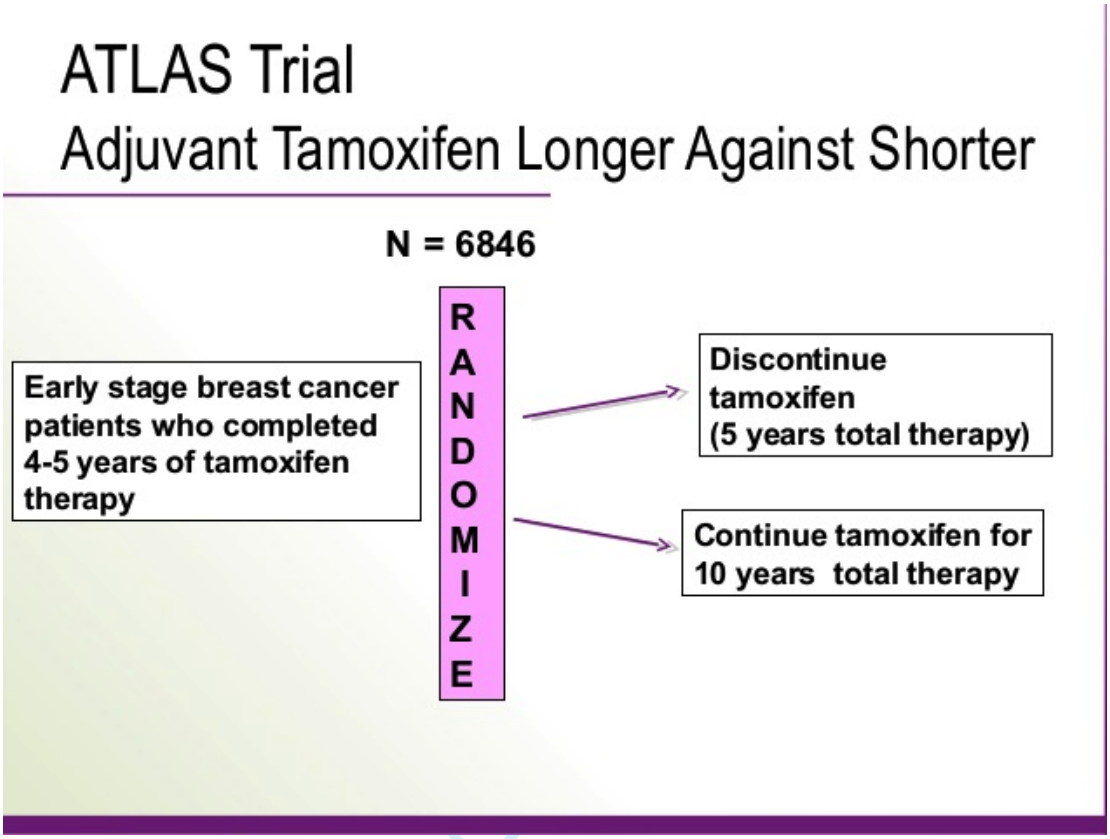
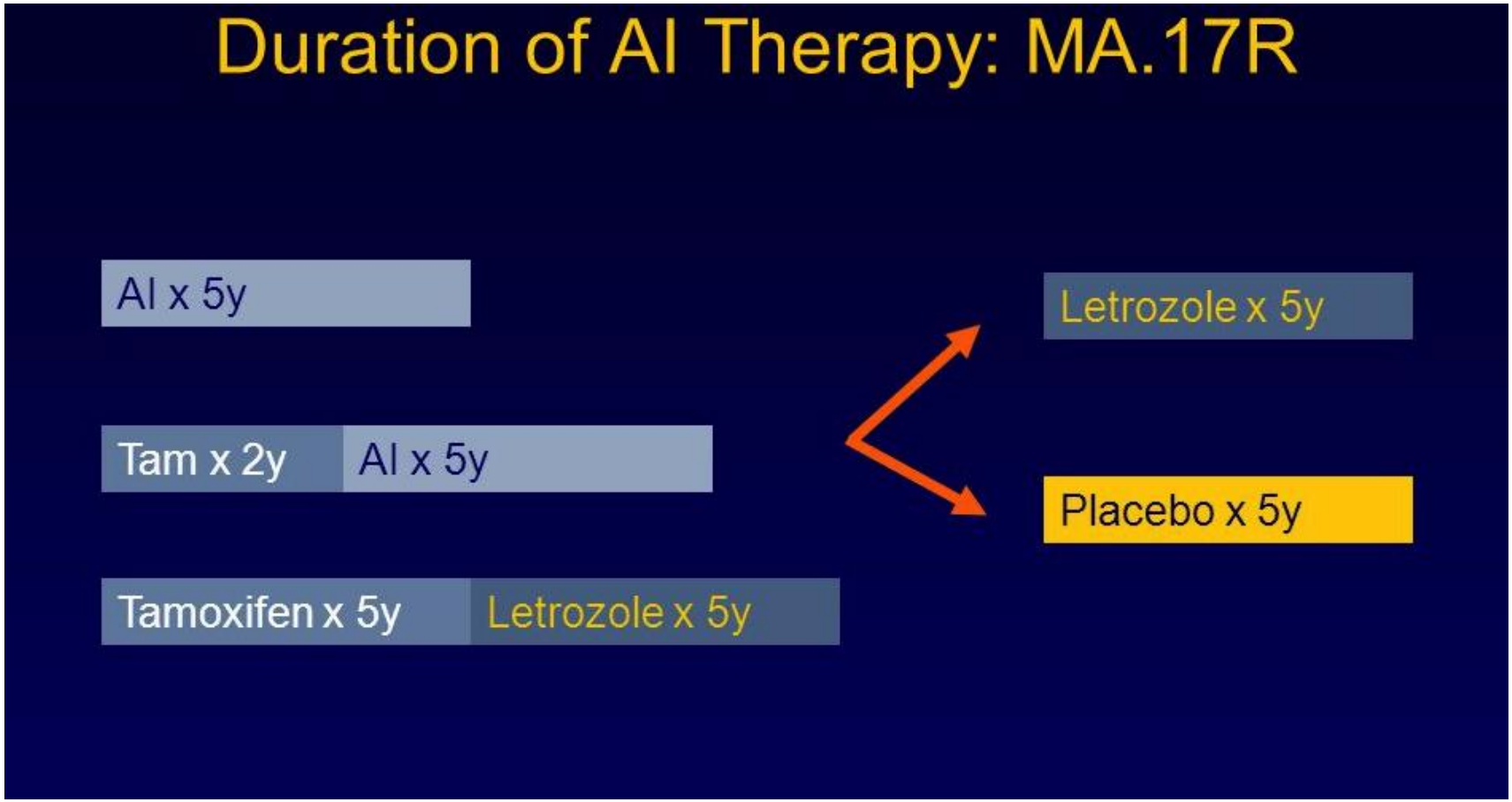
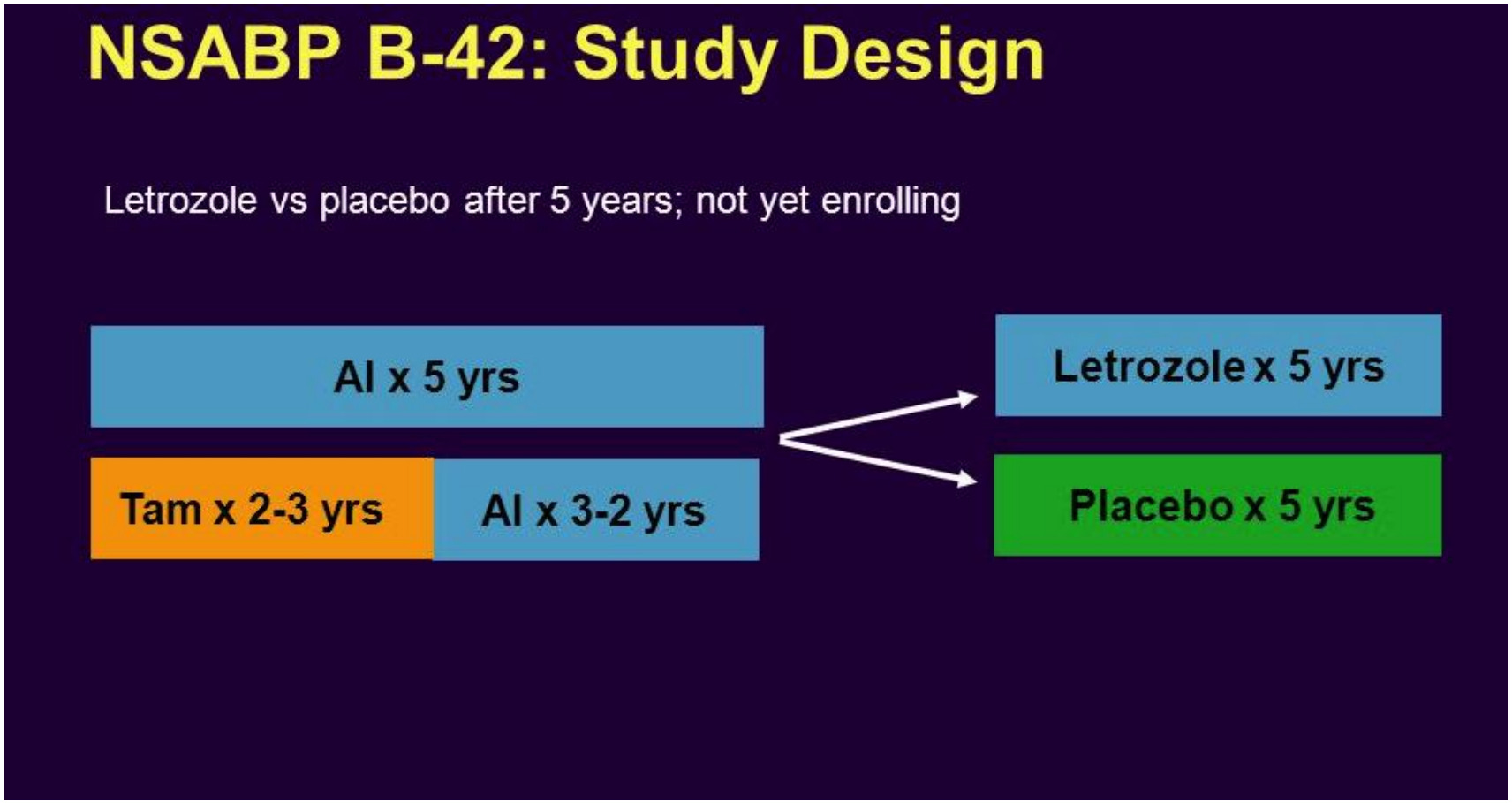



Duration of AI Therapy: MA.17R
AI x 5y
Tam x 2y
AI x 5y
Tamoxifen x 5y
Letrozole x 5y
Letrozole x 5y
Placebo x 5y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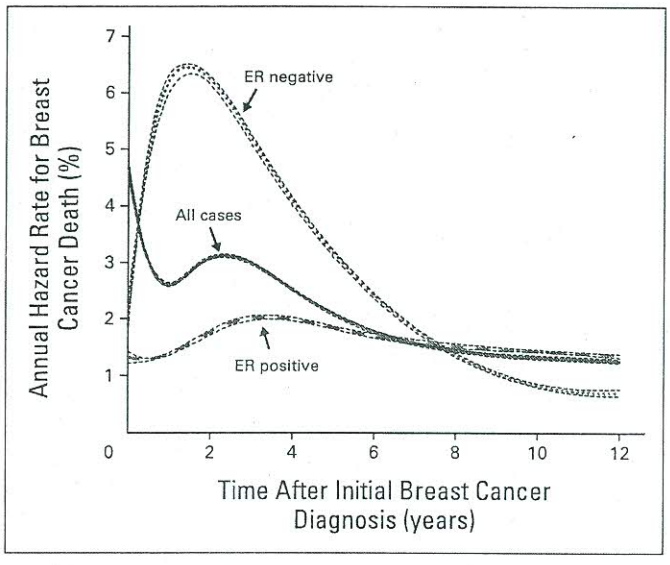
AI x 5 yrs
Tam x 2-3 yrs
AI x 3-2 yrs
Letrozole x 5 yrs
Placebo x 5 yrs


Annual Hazard Rate for Breast Cancer Death (%)
7
6
5
4
3
2
1
0
2
4
6
8
10
12
ER negative
All cases
ER positive
Time After Initial Breast Cancer Diagnosis (years)

Introduction

Over the past two decades hormonal therapy for early stage breast cancer has become increasingly complex and no longer are patients offered the ubiquitous 5 years of tamoxifen therapy with or without ovarian suppression for pre-menopausal women. With the advent of aromatase inhibitors, there is now uncertainty about the optimum schedule for adjuvant systemic hormonal therapy in terms of choice of agent and duration of usage [1]. Risk stratification is being used to determine type of hormonal agent and whether patients should receive a standard course of 5 years total duration or 'extended' endocrine therapy up to 10 years. It should be noted that there is a significant risk of relapse for many hormone receptor positive breast cancers with half of these cases occurring beyond 5 years and recurrence risk continuing to increase throughout the first 20 years of follow up. Indeed, the hazard plots for breast cancer death indicate that patients with oestrogen receptor (ER) negative tumours have greater risk of death from breast cancer than do patients with ER positive tumours during the initial 8 years following diagnosis [2]. However, after that 8 years period, the risk of breast cancer death is greater for patients with ER positive tumours when compared to those with ER negative tumours. Eight years following initial breast cancer diagnosis, the annual risk of breast cancer death for patients with ER positive tumours plateaus at about 1-2% per year. Thus, delayed recurrences are more concerning for patients with ER positive breast cancers than those with ER negative tumours [FIGURE 1]. There is a substantial risk of recurrence in absolute terms for smaller node negative tumours (T1N0) in years 15 to 20 after initial diagnosis of breast cancer [2]. This justifies exploration of extended endocrine therapy as a clinical strategy.

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tamoxifen as standard adjuvant hormonal therapy for the majority patients prior to widespread incorporation of aromatase inhibitor therapy into adjuvant hormonal schedules [4,5].

2) Aromatase inhibitors – these agents were initially employed in the treatment of advanced breast cancer and offered advantages over tamoxifen and progestins that were commonly used as first and second-line therapies respectively. Aromatase inhibitors have been applied in the adjuvant setting as upfront therapy for a standard treatment period of 5 years or sequenced as part of an early 'switch' strategy after initial treatment with tamoxifen for 2 – 3 years. No particular sequencing schedule has yielded any overall advantage but an aromatase inhibitor should be incorporated into the adjuvant hormonal schedule of all post-menopausal hormone receptor positive breast cancer patients. Those patients deemed to be at higher risk of relapse may derive most absolute benefit from an upfront aromatase inhibitor whilst for those with a lower hazard rate for relapse, an early switch policy may suffice with tamoxifen for the first 2 – 3 years followed by an aromatase inhibitor [6 – 10]. Benefits in terms of disease-free and overall survival must be balanced against longer term adverse effects on bone health and cognitive function as well as cost. Some patients at very low risk of relapse may derive minimal additional benefit from incorporation of an aromatase inhibitor into their treatment schedule and should receive tamoxifen only. Large randomized clinical trials such as BIG 1-98 have confirmed that 5 years of an aromatase inhibitor is better than tamoxifen for 5 years with gains in both recurrence and mortality [7,8]. Furthermore an aromatase inhibitor (2 – 3 years) sequenced after tamoxifen (2 – 3 years) is an alternative to 5 years of an aromatase inhibitor with a formal meta-analysis demonstrating lower rates of recurrence for aromatase inhibitor therapy (approximately 20% proportional reduction) and a small mortality gain. The overall survival benefit at 8 years was 1.7% in favour of aromatase inhibitors [11].

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Although the benefits of breast cancer adjuvant systemic therapy were generally assumed to be constant (i.e. proportional) over time, an analysis of 19 adjuvant systemic therapy trials in the National Surgical Adjuvant Breast and Bowel Project (NSABP) database indicate that treatment benefits diminish significantly at specific time points following surgery [12]. This suggests that the benefits of adjuvant systemic therapy may often reduce after cessation of therapy, and provides a rationale for consideration of extended adjuvant therapy for some subsets of patients.

Trials of extended tamoxifen therapy

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial randomised patients after surgery to 5 years of tamoxifen or placebo, and showed a statistically significant disease-free survival (DFS) and overall survival (OS) benefit for tamoxifen. To address the question of optimum duration of therapy, patients in the NSABP B-14 study who were alive and disease-free after 5 years of tamoxifen were then again randomised to an additional 5 years of tamoxifen or placebo. In the NSABP B-14 trial, there was no overall benefit from more prolonged therapy in a group of node negative patients with early stage breast cancer. The risks associated with more prolonged therapy that include thromboembolism and endometrial carcinoma, were considered to outweigh any benefits and indeed a small decrease in disease-free survival was documented [13,14]. A similar comparison was undertaken in the larger ATLAS (Adjuvant Tamoxifen – Longer against Shorter) trial involving almost 7000 patients who had received the standard 5 years of adjuvant tamoxifen therapy were randomized to continue tamoxifen for a further 5 years or stop (control group) [15] [FIGURE 2]. In contrast to the NSABP B-14 study, this revealed an impact on mortality from longer duration of tamoxifen usage amongst hormone receptor positive patients with statistically significantly fewer recurrences in the group receiving 10 years of tamoxifen therapy (rate ratio (RR) = 0.75) at a mean follow up of 7.1 women years. Interestingly, there was a less extreme effect of more prolonged treatment during years 5 - 9 (RR 0.90) with benefit and divergence of curves occurring mainly after year 10 (i.e. whilst not receiving active treatment). There was a significant reduction of breast cancer mortality with a rate ratio of 0.71 and an absolute reduction of 2.8%. These benefits were evident after year 10 of

follow up and were additional to any 'carry over' effect that is evident during years 5 – 10 but has largely disappeared after 10 years. There was no excess of uterine cancer deaths in pre-menopausal women and for those over 50 years of age the incidence of uterine cancer was 2.6% versus 1.6% (2p = 0.08), representing a net loss from endometrial cancer of 0.2%. The smaller aTTom trial revealed a more modest effect on mortality from 10 years of tamoxifen at 15 years with a hazard ratio of only 0.85 [16].

Trials of extended therapy with tamoxifen and an aromatase inhibitor

The seminal MA.17 trial was the first to explore extended endocrine therapy involving administration of an aromatase inhibitor (letrozole) after completion of a standard 5 years of tamoxifen therapy. This sequence of extended endocrine therapy with a combination of tamoxifen and an aromatase inhibitor led to improved disease-free survival with a marked reduction in the hazard ratio [HR= 0.52]. Moreover, there was a significant survival advantage for node positive patients [HR = 0.61]. Of note, this schedule involving an aromatase inhibitor was effective for women who were initially pre-menopausal but subsequently become post-menopausal during the period of treatment [17,18].

The MA.17R trial randomized patients to either 5 years of letrozole or 5 years of placebo following an initial 5 years of treatment that included one of the following options[FIGURE 3] [19]:

a) aromatase inhibitor for 5 years
b) early switch of tamoxifen (2-3 years) followed by an aromatase inhibitor (2-3 years)
c) receipt of more than 5 years treatment as per MA.17 protocol

At a median follow up of 6.3 years, trial results showed an increase in disease-free survival with an absolute benefit of 4% (letrozole arm = 95%; placebo = 91%). There was a relative decrease in risk of recurrent disease of 34% [HR 0.66; p = 0.01]. A noteworthy observation from this trial of extended endocrine therapy was an increase in bone fractures (14% versus 9%; p = 0.001) and more cases of new onset osteoporosis (11% versus 6%; p<0.001) for those randomized to receive additional endocrine therapy with letrozole [19].

Results of several other trials of extended hormonal therapy were reported concurrently at the San Antonio Breast Cancer Symposium (SABCS) in December 2016. Despite being eagerly anticipated, these trials were largely negative in terms of clinical outcomes and tempered enthusiasm for extended therapy in the immediate aftermath of these presentations. The DATA study compared 3 versus 6 years of anastrozole (1mg daily) following 2 – 3 years of tamoxifen therapy in hormone receptor positive early stage breast cancer [20]. The trial randomized 1912 post-menopausal women with oestrogen (ER) and progesterone receptor (PR) positive breast cancer who remained disease-free after an initial treatment period of 2 – 3 years with tamoxifen. The number of women receiving 3 and 6 years of anastrozole was 823 and 827 respectively on an intention-to-treat basis. The primary outcome measure was adapted disease-free survival for any cancer event including invasive or non-invasive cancer recurrence (local, regional or distant), second non-breast primary cancers and death from any cause. Adapted referred to survival beyond 3 years after randomization as all patients received the same endocrine treatment for this initial time period. The secondary endpoint was overall survival. Analysis of results revealed no significant difference in adapted disease-free survival at 5 years between treatment groups (79.4% for 3 years versus 83.1% for 6 years [HR 0.79 (CI 0.62 – 1.02); p = 0.07]). Furthermore, there was no impact of more prolonged anastrozole therapy on overall survival [HR 0.91 (CI 0.65 – 1.29); p = 0.6]. Notwithstanding these negative outcomes for extended therapy, subgroup analysis revealed a significant improvement in adjusted disease-free survival for larger node positive tumours (ER/PR positive, HER2 negative) in receipt of chemotherapy [HR 0.58 (CI 0.39 – 0.89); p = 0.01]. Prolonged anastrozole therapy was associated with increased morbidity from a range of symptoms including arthralgia/myalgia (58% versus 53%), osteoporosis/osteopenia (21% versus 16%) and arterial thrombotic events. It was concluded that there was no net benefit from extended endocrine therapy for most patients with early stage breast cancer.

The IDEAL trial likewise randomized almost 2000 patients to receive either 2.5 year or 5 years of letrozole (2.5mg daily) following an initial 5 years treatment period involving several endocrine options [21]:

a) tamoxifen for 5 years
b) early switch of tamoxifen (2-3 years) followed by an aromatase inhibitor (2-3 years)
c) aromatase inhibitor for 5 years

Hence some patients within this trial could potentially be treated with up to 10 years of an aromatase inhibitor and this may have relevance to current treatment recommendations for type and duration of adjuvant endocrine therapy. The primary and secondary endpoints for this study were disease-free and overall survival respectively. A comparison of results at a median follow up of 6.5 years failed to show any statistically significant differences for either trial endpoints or the metastasis-free interval. Thus hazard ratios for disease-free and overall survival were 0.96 (CI 0.76 – 1.20; p = 0.70) and 1.08 (CI 0.81 – 1.45; p = 0.59) respectively. In terms of side effects, this study reported a comparably high incidence of toxicity for both groups of 70% that included symptoms of arthralgia, myalgia, bone fracture and osteoporosis/osteopenia. In particular the authors attributed a low number of events to extended therapy and once again this has relevance to treatment guidelines. The equivalence of clinical outcomes within this trial led to the conclusion that there is no justification for extending aromatase inhibitor therapy beyond 2.5 years for the majority of patients (subgroup analysis did not identify any patients benefiting from 5 years of extended therapy). Thus a total of 7.5 years of sequential therapy with tamoxifen/aromatase inhibitor or aromatase inhibitor monotherapy is sufficient and should not be extended out to 10 years [21].

The NRG/NSABP B-42 study was the third in this trilogy of trials on extended endocrine therapy to be presented at the SABCS2016. This large trial randomized almost 4000 post-menopausal hormone receptor positive women to receive 5 years of letrozole or placebo after 5 years of endocrine therapy consisting of either an upfront aromatase inhibitor (5 years) or an early switch policy as for the DATA and IDEAL trials [FIGURE 4] [22]. Patients were recruited between September 2006 and January 2010 with half being node positive and one-third of patients aged less than 60 years. At a median follow up of 6.9 years there was a reduction in the primary endpoint of disease-free survival in favour of letrozole but this was not deemed to be statistically significant due to adjustment of the

pre-defined 2-sided p-value to 0.0418 from four interim analyses (alpha spending). As a consequence of this statistical ploy, the hazard ratio of 0.85 was no longer below the stipulated p-value for level of significance. There was no benefit for the secondary endpoint of overall survival (p= 0.22) but extended treatment with letrozole was associated with an improvement in the breast cancer-free interval [HR 0.71; p=0.003] – this included recurrence and contralateral disease. In addition, there was improvement in the cumulative incidence of distant recurrence [HR 0.72; p=0.03]. Although the reduction in disease-free survival is statistically non-significant in a formal sense, it might be argued that results of this NSABP B-42 trial are concordant with those of MA.17R for which a clinically meaningful improvement in this primary endpoint was demonstrable. Interestingly, no increase in numbers of osteoporotic fractures attributable to extended endocrine therapy was found in the NSABP B42 trial. It has been pointed out by Mamounas that these two trials are 'more similar than different' and collectively supportive consideration of extended endocrine therapy for selected patients taking account of patient preference, relapse risk and co-morbidities [23].

Results of the Austrian Breast Cancer Study Group (ABCSG) -16 trial were presented the following year at SABCS. This randomized phase III trial likewise involved almost 4000 patients (n = 3,484) and compared 2 years with 5 years of extended endocrine therapy (anastrozole, 1mg daily) [24]. After a standard 5 years initial treatment (tamoxifen or an aromatase inhibitor alone or sequenced), patients were randomized to one of these treatment groups with the primary endpoint being disease-free survival. The latter was almost identical with a similar proportion of patients (22%) developing recurrence or relapse irrespective of treatment allocation (2 years (377/757) versus 5 years (380/757)). The fracture rate was noted to be higher in years 3 to 5 leading to the conclusion that 2 years of extended therapy with anastrozole is sufficient for most patients and more prolonged treatment should not be recommended on the basis these trial data.

Further evidence in support of a small benefit from extended adjuvant hormonal therapy came from the Arimidex extended adjuvant randomized study (AERAS) conducted in Japan and presented at the SABCS in December 2018 [25]. This large multicentre study enrolled almost 1700 patients and examined the impact of an additional 5 years of the

aromatase inhibitor anastrozole following either an initial 5 year treatment span of either anastrozole or an early tamoxifen (2 years)/anastrozole (3 years) switch. Patients were randomised to stop anastrozole or continue for a further 5 years and compliance levels exceeded 70% in both arms of the trial. At a median follow up of 4.9 years there were statistically significant gains in both 5 year disease-free survival (91.9% versus 84.4% [HR 0.548; p = 0.004]) and distant disease-free survival (97.2% versus 94.3% [HR 0.514; p = 0.0077]) for continuation of endocrine therapy up to 10 years. These clinical benefits were most apparent in node positive patients, although all groups demonstrated significant improvements in outcomes (except for overall survival). Moreover, adverse side effects were more pronounced with extended therapy and included an increase in numbers of bone fractures (2.8% versus 1.2%) and osteoporosis (33% versus 28%) with more frequently reported arthralgia, joint stiffness and hot flushes.

Another trial similar in design to DATA and IDEAL was recently presented at the 2019 ASCO meeting; the Gruppo Italiano Mamella 4 (GIM4) multicentre trial randomised post-menopausal hormone receptor positive women with early breast cancer who were disease-free after 2 – 3 years of adjuvant tamoxifen to either 2 – 3 years (n = 1030) or 5 years (n = 1026) of letrozole (short and long arms respectively) [26]. With a median follow up of 10 years (IQR range 8.6 – 11.4), there was improvement in the primary endpoint of disease-free survival for extended therapy. Eight year disease-free survival rates were 80% (95% CI 77.3% - 82.7%) and 85% (95% CI 82.9 – 87.6) for the short and long arms respectively with a hazard ratio of 0.82 [p = 0.031]. Of note, there was no interaction between random assignment to the long and short arms of this trial and variables such as age, nodal status and tumour grade. Despite a significant increase in incidence of osteoporosis, there was no difference in fracture rate between the shorter and longer duration of endocrine therapy. Results of this GIM4 trial in terms of disease-free survival are therefore concordant with MA.17R and NSABP B42 (notwithstanding alpha spending).

Discussion

The results of the three aforementioned trials presented at SABCS2016 were a surprise to many and prompted a re-thinking of extended endocrine therapy for patients with early stage breast cancer. It is essential to balance any clinical benefit with potential side effects, patient wishes and costs. For these reasons, recommendations for extended endocrine therapy have become highly individualized and this is reflected in the looser language of formalized guidelines. There is an element of clinical uncertainty about how to use the current database to accurately and confidently select patients for more prolonged periods of endocrine therapy. Key factors to consider are higher disease stage, young age and patient preference together with adherence to prescribed medications. Biomarker information can potentially aid prediction of late recurrence and relevant genomic classifiers with clinical utility include Oncotype-DX, PAM50, Endopredict and Breast Cancer Index [27]. A retrospective comparison examined the performance of multi-gene signatures for prediction of late distant recurrence in node negative and node positive cases of breast cancer. The study focused on 6 signatures in clinical usage (Clinical Treatment Score [CTS], Immunohistochemical markers [IHC4], Oncotype Recurrence Score [RS], Breast Cancer Index [BCI], Prosigna [ROR] and EndoPredict [EPClin]) and was a pre-planned analysis of data from the Anastrozole or Tamoxifen Alone or Combined (TransATAC) trial. The additional prognostic value of each signature over and above clinical variables was assessed and risk stratification employed to identify groups most likely to benefit from biomarker information (based on calculation of likelihood ratios). For node negative patients, all signatures provided additional information over and above clinical/pathological, were good predictors of recurrence in years 0 – 10 and identified patients with a low risk of distant recurrence for whom the value of chemotherapy was limited. The signatures BCI, ROR and EPClin were good predictors for late recurrence with all signatures identifying patients with a low risk of late distant recurrence for years 5 – 10 for whom extended endocrine treatment was not justified. By contrast, for node positive patients, the BCI and EPClin specifically identified patients with a low risk of distant recurrence for years 0 – 10 for whom chemotherapy is of limited value. These two signatures also identified patients at low risk of late distant recurrence for whom extended endocrine therapy is probably not justified.

Therefore all 6 signatures can identify low risk node negative patients with limited capacity of BCI/EPClin to identify low risk node positive patients.

Extended endocrine therapy should be considered for most pre- and post-menopausal hormone receptor positive women receiving chemotherapy as these are more likely to be at high risk of relapse based on conventional clinical and pathological factors. There are two broad groups of patient to consider in the context of extended endocrine therapy. Firstly, those patients that have already embarked on a 5 year course of adjuvant hormonal therapy and secondly those patients with newly diagnosed breast cancer and no prior exposure to tamoxifen or an aromatase inhibitor. Within each of these groups there are defined categories of patients – low risk, pre-menopausal, peri-menopausal and post-menopausal. A particular concern about extended therapy relates to women who have received an aromatase only as adjuvant therapy; extended therapy should be considered cautiously for this group with attention to tolerability to-date, relatively young age (long life expectancy), bone health and possession of a contralateral breast.

For those patients coming to the end of a 5 years treatment span involving an early switch from tamoxifen to an aromatase inhibitor, then a reasonable option is to continue with the aromatase inhibitor for a total duration of 7.5 years (this would be supported by data from the IDEAL and ABCSG-16 trials). For those in receipt of 5 years tamoxifen only as a consequence of being low risk, then further endocrine therapy is not indicated. These patients have already survived 5 years and have a very good prognosis by virtue of histology and stage. Extended therapy should not routinely be offered in these circumstances unless demanded by the patient themselves. For a small number of women, continued treatment can be a ‘security blanket’ and stopping can trigger much distress (despite informed discussion of risks and benefits). For patients in receipt of 5 years of an aromatase inhibitor, extension of therapy out to 7.5 – 10 years should be considered (taking account of previously mentioned factors). It should be noted that there is no evidence at the present time supporting 10 years of an aromatase inhibitor and the IDEAL trial showed no benefit for disease-free nor overall survival but potentially included patients with 10 years of an aromatase inhibitor (no separate subgroup analysis based on

endocrine regime prior to randomization). Those women who are pre- or peri-menopausal and *not* low risk should receive 10 years of tamoxifen therapy based on results of the ATLAS trial.

Several endocrine treatment options exist for newly diagnosed breast cancer patients with hormone receptor positive disease and no prior exposure to tamoxifen or an aromatase inhibitor. For post-menopausal low risk women, 5 years of an aromatase inhibitor should suffice with tamoxifen an appropriate alternative when contraindications to an aromatase inhibitor are apparent (e.g. history of osteoporosis or low bone mineral density score consistent with a degree of osteopenia). For all other post-menopausal women, 10 years of an aromatase inhibitor should be prescribed with the default option of tamoxifen if not tolerated or there is radiological evidence of poor bone health. On the basis of current trial data discussed above, another option is to start post-menopausal patients on tamoxifen for 2 – 3 years and then change to an aromatase for 5 – 7.5 years – this would provide between 7.5 and 10 years of endocrine treatment in total. Once again, this might be appropriate when bone health is questionable or there is mild osteopenia. For pre-menopausal women below the chemotherapy threshold, 5 or 10 years of tamoxifen is recommended whilst 10 years would nowadays be prescribed routinely for those above the chemotherapy threshold. It is advisable to treat peri-menopausal women at presentation the same as pre-menopausal as measurements of hormone levels (e.g. follicle stimulating hormone) during or immediately after chemotherapy can be problematic.

A meta-analysis by the EBCTCG has attempted to clarify the issue of extended endocrine therapy and provide guidance to clinicians[28]. This analysis compared 3 groups of patients receiving either standard endocrine schedules (tamoxifen alone for 5 years [n=7,500], 5 years of an aromatase inhibitor alone [n=4,800] or 5 years of an early tamoxifen/aromatase inhibitor switch) or an extended schedule of the same for a total period of 10 years (n=12,500 for all sequenced combinations). Interestingly, this revealed a 24% overall reduction in risk of recurrence for extended therapy (9.5% versus 7.0%; $p<0.00001$) but was much higher when extended treatment with an aromatase inhibitor followed initial 5 year treatment period with tamoxifen compared with an aromatase

inhibitor (23%). This reduction was even less when duration of tamoxifen exceeded 5 years and duration of aromatase inhibitor therapy was correspondingly less (16%). The absolute gains in reduction of recurrence at 5 years risk for these 3 groups were 3.6%, 1.2% and 2.1% respectively (all statistically significant). Thus the impact of extended endocrine therapy is dependent on the type of therapy administered during the first 5 years with benefits greatest for those women in receipt of 5 years of tamoxifen and subsequently being switched to an aromatase inhibitor as part of an extended strategy. Not surprisingly, this meta-analysis found an increase in bone fractures for extended therapy (24%) with gains in clinical outcome being proportional to the extent of nodal involvement.

Conclusion

It is recognized that hormone receptor positive breast cancer has a long natural history characterized by a proclivity for chronic residual disease and late distant recurrence. Endocrine therapy acts upon cells in a cytostatic manner rather than killing cells and this is the rationale for prolonged therapy in order to maintain dormancy and suppress the process of 'kick-starting' foci of micrometastases. Nonetheless, trials to date of extended endocrine therapy have yielded modest results in terms of improving disease-free survival but highlighted disadvantages of more prolonged therapy in terms of side effects and costs. Once patients reach the 5 year time point from diagnosis, endocrine treatment options should be carefully reviewed taking account of several factors including intrinsic risk of disease recurrence, patient preference, tolerance of endocrine therapies to date and co-morbidities. Current recommendations favour up to 10 years of an aromatase inhibitor for most post-menopausal women at moderate to high risk with 5 years treatment only with either tamoxifen or an aromatase inhibitor confined to low risk pre- and post-menopausal women respectively.

Future Perspective

On the basis of evidence to date, there is likely a group of higher risk patients with larger tumours and positive lymph nodes that are likely to benefit from extended endocrine therapy in terms of clinical outcome measures. However, further follow up of current

trials is essential before any definitive conclusions can be made on the impact of extended therapy on risk of recurrence and in particular mortality. Increasing numbers of women are being treated with upfront aromatase inhibitors and this might limit the impact of extended endocrine therapy and indeed mortality reductions may be greater when an aromatase inhibitor is sequenced after 2 – 3 years of tamoxifen for a total treatment period of 10 years rather than 7.5 – 10 years of an aromatase inhibitor alone. This strategy would potentially minimise the adverse side-effects of aromatase inhibitors on bone health and joint symptoms and perhaps also be more cost-effective.

Executive summary

1) Several different options in terms of agent and duration of treatment are now available for adjuvant systemic hormonal therapy in women with hormone receptor positive early stage breast cancer.

2) Increasingly risk stratification is being used to determine both type of hormonal agent and whether treatment span should be the conventional standard of 5 years or extended for up to 10 years.

3) Risk of late recurrence is greater for hormone receptor positive tumours and can occur well beyond 10 years after initial diagnosis irrespective of tumour stage.

4) Longer term follow up data are now available on large numbers of patients treated with 5 years of tamoxifen only and these confirm significant impact on recurrence and mortality throughout the first 15 years of follow up.

5) The advent of aromatase inhibitors has transformed endocrine management of breast cancer but at the same time introduced an element of complexity and uncertainty that has been compounded by issues of extended therapy.

6) Large randomised trials have confirmed that 5 years of treatment that incorporates an aromatase inhibitor either alone or sequenced with tamoxifen is superior to tamoxifen alone in terms of clinical outcomes with an absolute survival benefit of 1- 2%.

7) Late recurrences and the reduction in benefit after cessation of adjuvant hormonal therapy has led to exploration of extended endocrine treatment schedules varying from 7.5 to 10 years in total duration.

8) Trials of extended therapy have generally involved sequencing of tamoxifen and an aromatase inhibitor rather than a prolonged period of monotherapy with either agent.

9) The ATLAS trial showed clear benefits for 10 years compared with the standard 5 years of tamoxifen therapy and extended treatment is now recommended for higher risk and some moderate/lower risk pre-menopausal women.

10) Any extended schedule for post-menopausal women should include an aromatase inhibitor either as monotherapy or sequenced after initial tamoxifen therapy for either 2 – 3 years or 5 years.

11) Results to-date from several trials of extended hormonal therapy have been mixed, with at best small benefits for the primary endpoint of disease-free survival that is most apparent in patients who have received at least 5 years of tamoxifen prior to an aromatase inhibitor.

12) Extended endocrine therapy should be considered in women at higher intrinsic risk of recurrence (especially with node positive disease) with a total treatment span of 10 years.

13) Clinical judgment on an individual patient basis is essential and should take account not only of recurrence risk but also tolerance of endocrine therapy in the first 5 years, bone health and patient preference.

14) Further follow up of extended endocrine therapy trials will provide greater confidence in current recommendations and justify and any cost implications from additional treatment.

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