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Controversies in adjuvant endocrine therapy for pre- and post-menopausal women with breast cancer

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ABSTRACT

Nearly 80% of breast cancer are hormone receptor positive. The efficacy of hormonal adjuvant therapy of breast cancer was expressed in the most recent EBCTG overview analysis of randomised trials using adjuvant tamoxifen. Five years of adjuvant tamoxifen led to proportional risk reduction, in terms of recurrence and mortality for hormone receptor positive patients, of 47% and 26%, respectively. This benefit was constant, regardless of menopausal status, age or whether or not chemotherapy was administered. More recent trials evaluating the use of aromatase inhibitors have challenged the standard of hormonal therapy in post-menopausal patients. However, many questions have been raised from these trials: (a) the optimal management of patients with hormone receptor positive breast cancer in terms of selection of hormonal agents and its sequence and duration; (b) the role of ovarian suppression in pre-menopausal patients; and (c) the actual role of biomolecular markers in clinical decision.
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1. Introduction

Hormone treatment of early breast cancer has a different approach according to menopausal status. In pre-menopausal patients, the usual treatment of hormone positive breast cancer is tamoxifen, with or without ovarian function suppression.[1] In post-menopausal patients with hormone positive breast cancer, aromatase inhibitors represent a good alternative to tamoxifen. These agents have been used in different strategies: after surgery (up-front),[2,3] or sequentially, that is after 2 or 3 years of tamoxifen (early switch),[4–9] or after 5 years of tamoxifen (extended switch).[10–13]

2. Tamoxifen as adjuvant hormonal therapy in pre-menopausal patients

Nearly 20% of all breast cancers occur in women younger than 50 years. Amongst them 60% show positive expression of both oestrogen (ER) and progesterone (PGR) receptors. The mainstay of adjuvant endocrine therapy in pre-menopausal patients is tamoxifen; its efficacy was first showed in multiple trials started in 1980s.[14–16] The most recent Oxford Overview underlines the efficacy of 5 years of tamoxifen in women with ER positive or unknown receptors, with 41% reduction of annual recurrence rate, 34% reduction of annual mortality and 39% reduction in the annual risk of controlateral breast cancer.[17] Moreover, this benefit is consistent and similar in women across age.[17] The duration of tamoxifen therapy beyond 5 years is still under investigation. In fact, the NSABP-B14 trial which enrolled women ER+, node negative, only 26% of whom younger than 50 years showed a worse disease free survival (DFS) with longer use of tamoxifen. A criticism to this trial could be that it enrolled only node negative patients, only a small part of them being under the age of 50, thus leaving uninvestigated the possible beneficial effect of longer tamoxifen therapy in node positive patients, i.e. in a population with an increased risk of recurrence.[18] An attempt to solve this question was done by the ATLAS trial (The Adjuvant Tamoxifen, Longer Against Shorter) which randomised

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11,500 women (59% ER+; 41% ER untested) who had completed 5 years of tamoxifen, to continue tamoxifen for 5 more years, or control. An update of this trial reported that there was no statistical difference in overall mortality between the two groups. However, continuation of tamoxifen beyond five years reduced recurrence rate, although longer follow-up is needed to assess long-term effects on mortality.[19]

Pre-menopausal patients included in the Oxford Overview have a reduction of annual risk of death of 38% with tamoxifen plus chemotherapy.[17] In the subgroup analysis of patients younger than 50 with ER+, the association of chemotherapy with tamoxifen showed a reduction of the recurrence rate at 5 years by 21.6% versus 14% for tamoxifen alone, with an absolute benefit of 7.6%.[17] However, the patients younger than 50 years included in the Oxford Overview were only 177, and the chemotherapy regimen used was not anthracycline based. More recently IBCSG (International Breast Cancer Study Group) trial 13-93 study randomised 1246 node positive pre-menopausal patients to receive tamoxifen for 5 years or not, after chemotherapy with anthracycline. DFS was better for chemotherapy plus tamoxifen in pre-menopausal patients with ER positive and high risk of recurrence, while no difference in OS emerged.[20] Chemotherapy amenorrhea was related to better DFS in patients with ER+ tumours, giving an indirect information on the importance of ovarian function suppression by chemotherapy. Moreover, no interaction was observed between tamoxifen and chemotherapy amenorrhea, thus indicating that iatrogenic amenorrhea must not be considered an alternative to tamoxifen.[20] IBCSG trial 11-93 investigated also on the possibility to avoid chemotherapy for pre-menopausal patients with ER+, intermediate risk according to St. Gallen criteria: randomising patients to chemotherapy plus ovarian ablation/suppression (OAS) and tamoxifen versus OAS plus tamoxifen. No difference in terms of DFS was evident across the arms. The trial closed prematurely due to its slow accrual, thus it resulted strongly underpowered to exclude the role of chemotherapy in these patients.[21] With regard to the timing of administration of tamoxifen, it was well established by SWOG INT 0100 study, in which post-menopausal patients treated with concomitant tamoxifen and chemotherapy showed a slightly worse DFS and OS as compared to patients treated with tamoxifen given sequentially to chemotherapy.[22]

3. Subgroups of adverse prognosis and benefit of hormonal therapy

Nearly 20% of ER+ breast cancers are PGR negative. The role of PGR has been investigated for a long time. Nowadays, it is generally accepted that ER+ PGR– patients identify a more aggressive subtype of breast cancer with a poor prognosis, perhaps correlated with a worse response to endocrine treatment. Clinical trials investigated the benefit of therapy in this subtype amongst post-menopausal patients, but no difference in the magnitude of benefit was seen.[23,24] In the same way the Her-2 over-expression identified a more aggressive phenotype of breast cancer due to a crosstalk between signal transduction pathways and related to tamoxifen resistance.[25] Until now there are no validated methods to select this subtype amongst a heterogeneous population in which, on average, the endocrine therapy has the same effects for all subgroups; therefore, today the same hormonal treatment must be given to all subtypes including those with PGR negative and Her-2+.

4. Timing and efficacy of ovarian ablation and suppression

Use of either ovarian ablation or suppression with a luteinising hormone-releasing hormone (LHRH) analogue gave a reduction of 30% in recurrence and breast cancer mortality both in women younger than 40 years and aged 40–49 years.[17] Moreover, this benefit is consistent across the years, underlining a sustained late effect with ovarian ablation. According to these findings, a still open question is if a short course of LHRH (2 or 3 years) could replace the permanent ablation. The Overview included trials in which all methods of ovarian ablation (radiation or surgical menopause) were considered and oestrogen receptor status was available. Recently, a meta-analysis based on individual patient data, including only trials with LHRH analogues and patients with hormone receptor positive, assessed the benefit of using LHRH analogue only.[26] The use of LHRH analogue as sole therapy did not give a reduction in risk of recurrence and death, probably for the small number of patients in this group, or for the short course of LHRH adopted. Similarly, LHRH plus tamoxifen did not affect the risk of recurrence on death, over tamoxifen alone[26] (Table 1). The addition of LHRH to chemotherapy or

Table 1 – Summary of findings of the LHRH agonists in early breast cancer overview group meta-analysis

Treatment	Recurrence			Death after recurrence		
	HR	95% CI	P	HR	95% CI	P
LHRH versus no therapy $n = 338$	0.72	0.49–1.04	0.08	0.82	0.47–1.43	0.49
LHRH + T versus T $n = 1013$	0.85	0.67–1.09	0.20	0.84	0.59–1.19	0.33
CT + LHRH versus CT	–24.7	–39.5 to –6.2	0.01	–27.3	–44.4 to –4.9	0.02
$\leqslant$40 years; $n = 714$						
$\geqslant$40 years; $n = 1.662$	–5.1	–20.1 to 12.7	0.55	–5.3	–24.2 to 18.3	0.63
CT + –T + LHRH versus CT + –T	–25.2	–39.4 to –7.7	0.01	–28.3	–44.9 to –6.8	0.01
$\leqslant$40 years; $n = 795$						
$\geqslant$40 years; $n = 1.946$	–3.9	–18.1 to 12.9	0.63	–7.5	–25 to 14.1	0.47
LHRH versus CT $n = 3184$	1.04	0.92 to 1.17	0.52	0.93	0.79 to 1.10	0.40

Abbreviations: LHRH, luteinising hormone-releasing hormone; HR, hazard ratio; CT, chemotherapy.

to chemotherapy plus tamoxifen did not reduce the hazard of recurrence, but a benefit was evident in the chemotherapy alone group for the patients younger than 40 years[26–28] (Table 1). LHRH meta-analysis compared chemotherapy versus LHRH alone and like previous studies that investigated the same comparison[29–32] did not find any difference in risk of recurrence or death independently by age[26] (Table 1).

We must consider that the LHRH meta-analysis and the previous studies that compare it to chemotherapy included mostly CMF as chemotherapy regimen, only 32% used anthracyclines-based regimen nor taxanes were used, none containing tamoxifen, resulting suboptimal in both arms.

5. Aromatase inhibitors in pre-menopausal patients

In pre-menopausal women, AIs have not been shown to be effective and indeed cause negative feedback to the pituitary gland, resulting in surges of oestrogens, which may be more likely to increase breast cancer cell growth than have beneficial effect.[33,34] Moreover, their use is not indicated in patients that have cessation of menses after chemotherapy, in fact during therapy with aromatase inhibitors it is possible a return of ovarian function causing at the same time a reduced anticancer efficacy and a risk of unwanted pregnancy. Caution must be taken also in patients nearly 50 years after many months of amenorrhoea. In these women, a strict monitoring of FSH, LH and estradiol must be done, in case of use of an AI.[35] Actually this question remains open and it is under investigation in two ongoing trials: (1) SOFT trial (suppression of ovarian function trial) randomised pre-menopausal patients treated or not with chemotherapy to receive tamoxifen for 5 years versus OAS plus tamoxifen for 5 years versus OAS plus Exemestane for 5 years and (2) TEXT trial (tamoxifen and exemestane trial) randomised patients node negative or low risk node positive, treated or not with chemotherapy, to receive 5 years of LHRH plus tamoxifen versus LHRH plus exemestane.[36–38]

6. Endocrine therapy for post-menopausal patients

Tamoxifen was the gold standard of endocrine therapy in post-menopausal patients for two decades. The use of tamoxifen was associated with a 41% relative reduction in the risk of recurrence and a 34% relative reduction in the risk of death in patients with ER+ or ER unknown tumours.[17] Aromatase inhibitors (AIs) suppress plasma oestrogen levels in post-menopausal patients by inhibiting or inactivating aromatase, the enzyme responsible for the synthesis of oestrogen from androgenic substrates. Anastrozole and letrozole are non-steroidal inhibitors (type I, reversible), whereas exemestane is steroidal (type II, irreversible).[33] The AIs were used in clinical trials with different modalities: soon after surgery (upfront), after 2 or 3 years of tamoxifen (early switch) and after 5 years of tamoxifen (extended switch).[2–13] ATAC (arimidex, tamoxifen, alone or in combination) trial investigated the role of anastrozole upfront versus tamoxifen in post-menopausal patients ER+. Recently, the results of this study, at a median of 100 months of follow-up, became available. Disease free survival, distant disease free survival, time to recurrence, time to distant relapse and incidence of controlateral breast cancer were significantly improved in the anastrozole arm; moreover, the lower recurrence rate was constant even after treatment was stopped. This suggests a carry-over effect of anastrozole whose activity seems to be prolonged beyond drug discontinuation.[2] However, the overall survival of anastrozole treated patients was not different from that of tamoxifen treated patients. The BIG 1-98 (Breast International Study Group) study randomised post-menopausal patients ER+ with breast cancer, to receive upfront tamoxifen for 5 years versus letrozole for 5 years, versus a sequence of the two drugs. The use of letrozole, as compared to tamoxifen, led to a reduction in the risk of an event comparable to that showed by anastrozole in the ATAC study[3] (Table 2). In fact, also in this trial, which has actually 51 months median follow-up, all efficacy end-points, unless overall survival, were achieved by letrozole. However, the results of the crossover arms are still not available.

The design of sequential trials is based on pre-clinical models in which prolonging tamoxifen exposure caused acquired resistance,[39,40] so the use of a non-cross-resistant agent could be superior to tamoxifen alone. The largest trial on this basis is the IES (Intergroup Exemestane Study) trial, which randomised post-menopausal patients after two or three years of tamoxifen to continue tamoxifen or to switch to exemestane, for a total of 5 years.[4,5] DFS and OS were better for the switch strategy.[5] Other studies with the same design, such as Austrian Breast and Colorectal Cancer Study Group (ABCSG), Arno 95 and ITA study showed a better DFS and OS (unless for the ABCSG trial) for switching to anstrozole after 2 or 3 years of tamoxifen[40] (Table 2). Moreover, a meta-analysis based on individual patient data of trials with early switch strategy only, gave an absolute benefit of OS that is about 3%.[41]

Given the risk of recurrence during the 15 years after the diagnosis of breast cancer, an extended strategy was investigated. MA-17 trial randomised women after 5 years of

Table 2 – Efficacy data from trial comparing AI in different strategies to 5 years of tamoxifen

Trial	AI	Outcome measure	HR	95% CI	P value
Upfront trials					
ATAC	A	DFS	0.85	0.76–0.94	0.003
BIG 1-98	L	DFS	0.82	0.71–0.95	0.007
Switching trials					
IES	E	DFS	0.76	0.66–0.88	0.0001
ABCSG8/ARNO 95	A	EFS	0.60	0.44–0.81	0.0009
ITA	A	DFS	0.57	0.38–0.85	0.005
Extended trials					
MA17	L	DFS	0.58	0.45–0.76	<0.001
ABCSG 6a	A	EFS	0.64	0.41–0.99	0.048

ATAC, arimidex, tamoxifen alone or in combination trial; BIG 1-98, breast international group; IES, intergroup exemestane study; ABCSG, Austrian Breast Cancer Study Group.

tamoxifen to 5 years of letrozole versus placebo. DFS was better for patients in the letrozole group and a survival benefit was seen amongst node-positive patients.[10,13] There are no data about the toxicity of AIs after 5 years and more information is needed to establish the safety of a prolonged treatment.[13] NSABP B33 and ABCSG trial 6a showed in the same way a beneficial of the extended therapy after five years of tamoxifen, for exemestane and anastrozole, respectively[11,12] (Table 2).

7. Selection of therapy in post-menopausal patients

The main question in this population is the way to use AI, upfront or sequential. The trials in which is present a small benefit for OS are only the sequential trials: IES(5) study, MA17 for the subgroups with node positive,[12] the ARNO study, the meta-analysis of ABCSG/ARNO and ITA studies.[6–8] The principal criticism to these studies is that they do not consider the recurrence occurred in the first two years because the randomisation is performed after 2 or 3 years of tamoxifen; moreover, they differ about the definition of DFS. Until the publication of the final data from BIG1-98, there will be no data to compare sequential strategy to upfront. Moreover, many attempts have been done to construct an indirect comparison of different strategies by mathematical models. Punglia et al.[42] provided a model to compare the two strategies and concluded that there is a modest survival benefit in favour of sequencing strategy. Another model proposed to explain the benefit of switching strategy is the so called deep model[43] suggesting that a proportion of hormonal receptors could become PGR negative under the exposure to tamoxifen; so in the context of a switching strategy it could be useful to use an AI after two or three years of tamoxifen. This hypothesis is not sustained by a recent evaluation in the context of BIG 1-98 trial of the efficacy of letrozole according to the expression of ER and PGR. In fact, this review did not confirm the status of PGR as determinant for response to hormonal therapy.[23] The risk of recurrence for breast cancer remains for several years after stopping hormonal therapy so the extended strategy could be a reasonable option to reduce this risk. Two studies have showed a benefit to prolong therapy after 5 years,[10–13] but they differ about the definition of endpoints and actually we do not have a validate method to identify which patient is at a major risk of late recurrence; so the extended therapy with AIs must not be considered a standard therapy. Moreover, we must consider the profile of toxicity of AIs and the potential risk with its prolonged use.

8. Safety profile of endocrine therapy

Many side-effects of endocrine therapy, such as hot flushes and mood disturbances, are related to oestrogen deprivation and are common to tamoxifen and AIs, reflecting the mechanism of action of these drugs. In addition, tamoxifen has oestrogenic effects that are beneficial in some tissues: tamoxifen lowers serum cholesterol levels and protects against bone loss and cardiovascular disease, but is also associated with potentially life-threatening side-effects, such as endometrial cancer and thromboembolic disease. As AIs lack oestrogenic activity, they are not associated with these serious adverse events. Clinical trials comparing AIs with tamoxifen in the adjuvant setting have shown that AIs are well tolerated and are associated with a lower incidence of gynaecological symptoms and hot flushes than tamoxifen. However, AIs are associated with musculoskeletal side-effects, such as arthralgia, myalgia and bone loss, but these events are preventable or manageable. The effects of AIs on lipid metabolism and the cardiovascular system are still debatable, but placebo-controlled trials provide no evidence to suggest that AIs adversely affect these systems. It is worth of note, as demonstrated in the ATAC 100 months results update, that the increase in fracture rate, a side-effect expected during use of anastrozole, dramatically decreased after drug discontinuation.[2]

9. Conclusion

In pre-menopausal patients, tamoxifen in association with a longer use of LHRH is the gold standard especially for patients that continue to menstruate after chemotherapy, although it is actually not possible to identify subgroups in which the hormonal therapy has a little benefit. Aromatase inhibitors must be used with caution in pre-menopausal patients amenorrheic after chemotherapy because of the potential recovery of ovarian activity.

In post-menopausal patients we are waiting for more data to identify the better strategy to use AIs, upfront or switching strategy, actually both results valid. We need more data to extended therapy with AIs after 5 years and if we decide to prolong therapy we must outweigh benefit and risk of toxicities. Thus, methods for improving the use of endocrine therapy, such as exploring new classes of agents, dosing, scheduling, combinations, and the addition of targeted agents to reduce the development of resistance, are crucial for the next future.

Conflict of interest statement

All authors disclose no financial and personal relationship with other people or organisations that could inappropriately influence this work.

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