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REVIEW ARTICLE

Adjuvant therapy with aromatase inhibitors in postmenopausal, estrogen receptor-positive breast cancer patients: upfront or sequential?

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Summary

For decades tamoxifen (TAM) has been the mainstay hormonal treatment for estrogen receptor positive (ER+) breast cancer patients. Nevertheless, during the last years, for postmenopausal women particularly, the third generation aromatase inhibitors (AI) became the preferred alternative. The results of the randomized trials showed that AI were superior to TAM in terms of efficacy, and were accompanied by a different but fairly convenient side effects profile. Subsequently, all updated guidelines recommend the use of AI in the adjuvant setting for this category of patients, either upfront, following 2-3 years of TAM or as extended adjuvant therapy, after 5 years of TAM. However, no consensus has been reached regarding the best strategy to be used, and the expert opinion is divided, based on the available evidence. The controversial aspect of whether AI should be used upfront or following 2-3 years of TAM is further detailed in this manuscript, and some useful recommendations are provided in order to facilitate the decision-making process during the current clinical practice.

Key words: adjuvant setting, aromatase inhibitors, breast cancer, estrogen receptor positive, postmenopausal, tamoxifen

Breast cancer is the most prevalent malignancy among women, with around 430,000 new cases registered yearly in the European Union [1]. The majority of the patients presents with the disease in early stages and are candidates for postoperative adjuvant systemic treatment. For decades TAM has been the gold standard for adjuvant hormonal therapy in patients with ER+ tumors. TAM induces a 15% absolute reduction in the recurrence and 9% improvement in overall survival (OS) rate at 15 years after diagnosis [2]. During the last years AI have been introduced as an alternative or complementary treatment for TAM in postmenopausal, ER+ patients. Strong rationale supports this trend as TAM and AI are substantially different in terms of clinical efficacy, side effects profile, mechanism of action and drug resistance [3-7]. In the metastatic disease setting the use of AI induced superior progression-free survival rates when compared with TAM [8,9]. Similarly, AI proved to be superior to TAM in the adjuvant setting, and subsequently they became a major therapeutical option of the adjuvant hormonal therapy. The ASCO guidelines are quite authoritative on this issue, stating that "adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor" [10]. Nevertheless the guideline is not conclusive with respect to which specific strategy to be followed since 3 different trial designs have been used to compare AI with TAM. The "upfront" design compared AI vs. TAM for 5 years [11-16]; the "early switch" design compared 5 years TAM with 2-3 TAM followed by AI [17-19]; and the "extended adjuvant" design compared 5 years TAM followed by placebo or AI [20,21] (Figure 1).

The extended adjuvant strategy will not be addressed in this manuscript due to the fact that the premature interruption of the MA 17 trial [21] makes the definitive conclusions controversial. Moreover, the recently presented data of the ATLS trial showed that 5

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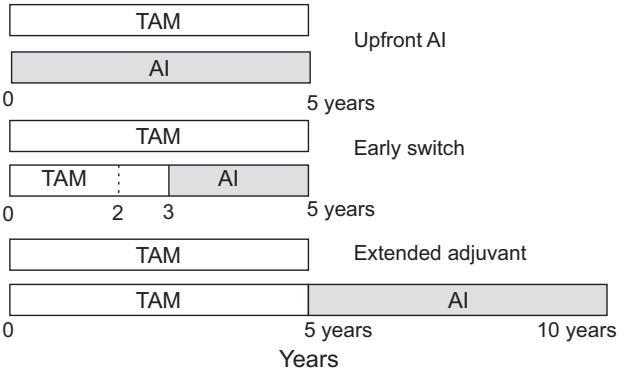

Figure 1. Clinical strategies evaluating the aromatase inhibitors (AI) vs. tamoxifen (TAM).

Table 2. Metaanalysis evaluating the disease-free and overall survival reported in the upfront and early switch aromatase inhibitors trials (adapted from [28])

Strategy		*No. of patients included*	*RR*	*p-value*	*Absolute benefit*
Upfront	DFS	11163	0.86	0.0004	2.3
	OS	11163	0.86	0.41	–
Early switch	DFS	8776	0.76	<0.0001	3.5
	OS	8776	0.76	0.003	1.6

RR: relapse risk, DFS: disease free survival, OS: overall survival

years of adjuvant TAM might not be a relevant control arm, as 10 years of TAM was related to a better outcome [22]. This paper will focus on the efficacy endpoint only, as the issues related to the side effects and cost differences deserve special considerations [23,24].

Starting the overview, it is imperative to stress that the use of adjuvant AI in postmenopausal ER+ patients was associated with a statistical improvement in disease-free survival (DFS), equally as if the treatment was started upfront or sequentially, after 2-3 years of TAM. On the other hand, most of the "early switch" trials showed also a trend toward an improvement in OS [17,25-27], whereas both upfront studies were negative in this regard after more than 5 years of follow up [14,16] (Table 1). A recently presented meta-analysis reinforced the individual trial results [28] (Table 2). One can conclude that the early switch strategy is better, as both major endpoints (OS and DSF) were significantly improved. The main drawback of this conclusion is related to the timing of the cancer and non cancer-related events taken into account. In the upfront trials all events were considered from the start of therapy, whereas in the switch trials the events during the initial TAM period were excluded and only patients without an early relapse have been analysed. This aspect becomes more relevant if the natural relapse rate of ER+ patients is considered. Two time-related peaks of the breast cancer relapses have been identified: one between years 2-3, and the second starting 5 years after diagnosis [29]. The upfront strategy supporters would argue that preventing the early relapse risk using a more active treatment (AI), seems more rational. How can we reconciliate these fairly confounding data in the current clinical practice? Definitely, a handy strait cut answer is missing, and the issue is highly controversial. Nevertheless, some rationale for the current practice use could be elaborated.

Firstly, we can start with the following hypotheses generating assumptions based on the previously presented data: a) patients treated with TAM and passing over the first relapse peak (2-3 years) would derive a survival benefit from adjuvant AI; b) the time to recurrence could be important (early vs. delayed relapse pattern); c) the ER+ tumors might be biologically heterogeneous; and d) the switching strategy alters the tumor biology (making the tumor more sensitive to the AI action).

Secondly, we should remember that adjuvant systemic therapy for ER+ patients is based equally on hormonal therapy and chemotherapy (CT) intervention. At years 3 and 5, the absolute difference in DFS favoring anastrozole (ANA) vs. TAM in the ATAC study was 1.6% and 2.5%, respectively [14]. For the same periods and same category of patients, adding CT to TAM pro-

Table 1. Disease-free and overall survival reported in the upfront and early switch AI trials

Strategy	*No. of patients included*	*DFS*		*OS*	
		HR	*p-value*	*HR*	*p-value*
Upfront					
ATAC [14]	6186	0.79	0.0005	0.97	0.70
BIG 1-98 [16]	4922	0.82	0.007	0.91	0.35
Switch					
IES [17]	4724	0.68	<0.0001	0.83	0.05 (ER+)
ABCSG [25]	2579	0.68	0.017	0.93	0.73
ARNO95 [26]	979	0.62	0.024	0.48	0.03
ARNO/ABSCG/ITA [27]	4006	0.59	<0.0001	0.71	0.04

AI: aromatase inhibitors, DFS: disease-free survival, OS: overall survival, HR: hazard ratio, ER: estrogen receptor

vided an absolute benefit of 4.4% and 4.9% over TAM alone [2]. One may conclude the following: a) adding CT to TAM doubled the 5 year DFS benefit compared with AI; and b) in the years 0-3 CT provided 90% of the benefit whereas AI only 46%. As such, according to the available data, patients receiving adjuvant CT+TAM have more substantial chance to overcome the first relapse peak of their natural breast cancer history.

On the other hand, one may argue that CT is not mandatory for all patients, especially for those with ER+ tumors. According to the last St. Gallen consensus, patients with low risk, ER+ tumors, could be spared of adjuvant CT. The low risk was defined as a bunch of good prognostic factors: node-negative, pT ≤ 2 cm, grade 1, absence of peritumoral invasion, HER 2/neu negative, and age ≥ 35 years [30]. All low risk factors should be present in order to qualify the patient for hormonal therapy as the sole adjuvant therapy. As the patient population in the upfront trials is stratified according to the individual prognostic factors, it is rather impossible to identify the patients clustering all the good prognostic factors [14,16]. Nevertheless, around 40% of patients in both trials [14,16] had node-positive disease, and should currently have received adjuvant CT. Of the remaining 60% node-negative patients, some 60% were also candidates for adjuvant CT due to other negative prognostic factors [31]. One may conclude that around 75% of the patients included in the upfront AI trials should have received adjuvant CT, while the actual CT delivered ratio was 21% in the ATAC and 25% in the BIG 1-98 study [14,16]. Taken together, these data imply the idea that in the upfront trials almost 50% of the patients were inappropriately treated with respect to the CT delivery. This discrepancy related to the CT administration should be considered as a very potent confounding factor. For instance, in the ATAC trial a significant interaction between the CT and the DFS benefit was documented over time. After a median follow up of 33 months, patients receiving CT actually had a better DFS when treated with TAM and not with ANA (hazard ratio/HR >1, favoring TAM) [11]. A longer follow up evaluation showed that the interaction between CT, type of hormonal therapy and the DFS benefit is time-dependent. At 47 months, for patients receiving CT, there was no benefit for any hormonal therapy (HR=0.98), whereas at 68 and 100 months there was a non-significant trend (HR=0.89) toward more benefit for ANA over TAM [14,32]. Of note, the HR difference did not reach statistical significance in the CT group at any time, whereas for patients not receiving CT, the HR for DFS was statistically significant favoring ANA at all time points analysis [32]. On the other hand, the BIG 1-98 data showed a pretty different picture. Two time points analyses have been performed: at 25 and 51 months. For patients receiving CT, the effect of letrozole over TAM seemed to be more consistent early in the course of the disease (HR=0.70, p=0.01) and less powerful, but still significant at 51 months (HR=0.74, p=0.03) [15,16]. By contrast, for patients not receiving CT the HR for DFS favored letrozole but was statistically not significant at both time points analysis (HR=0.85, and HR=0.86) (Table 3).

The interaction between CT and hormonal treatment in the switching strategy trials is hard to assess, mainly due to the fact that the events were counted after 2-3 years of TAM treatment. In the IES trial, with 30% of patients receiving CT, time and the CT delivery seemed not to influence the general outcome. Data were evaluated at 35 and 58 months of follow up, showing a statistically significant improvement of DFS regardless of the CT delivery (Table 3). All the above mentioned data point towards a careful evaluation of the confounding impact of CT over hormonal therapy benefit, and this aspect should be considered while interpreting the results of various adjuvant hormonal trials.

New data are supporting the concept of tailoring adjuvant treatment for ER+ tumors according to their genetic profile. The 21-gene recurrence score (RS) assay has been validated as an accurate tool for predicting prognosis and the benefit of adding CT to

Table 3. Impact of time and chemotherapy on the disease-free survival in the upfront and early switch trials

Strategy				*Disease-free survival*							
				2-3 years		*4 years*		*5-6 years*		*9 years*	
				HR	*p-value*	*HR*	*p-value*	*HR*	*p-value*	*HR*	*p-value*
Upfront	CT	Yes	ANA	>1	NS	0.98	NS	0.89	NS	0.89	NS
			LET	0.70	<0.01	0.74	0.03	–	–	–	–
		No	ANA	<0.75	<0.05	0.75	<0.05	0.74	<0.05	0.71	<0.05
			LET	0.85	NS	0.86	NS	–	–	–	–
Switch	CT	Yes	EXE	0.69	<0.05	–	–	0.76	<0.05	–	–
		No		0.67		–	–	0.74		–	–

DFS: disease-free survival, HR: hazard ratio AI vs. TAM, CT: chemotherapy, ANA: anastrozole, LET: letrozole, EXE: exemestane, NS: non significant

TAM in ER+, lymph node-negative patients [34]. For the high recurrence score category (RS31) the addition of a CMF-like CT to TAM led to a 28% absolute decrease in 10-year distant recurrence rate (from 60 to 88%), and a HR=0.26 favoring the addition of CT. Conversely, there was no benefit derived from CT in the low RS category (RS<18). The likelihood ratio test for interaction between CT and RS was significant (p=0.038). In addition, individual multivariate models for the interaction between RS and CT adjusted for other variables (including patient age, tumor size, ER, PR, tumor grade) demonstrated the persistence of the strength of the interaction between RS and CT treatment (p=0.035) [34].

On the other hand, pharmacogenomics may identify women unlikely to benefit from adjuvant TAM. To become active, TAM should be metabolized to endoxifen via the cytochrome P450 2D6 (CYP2D6) enzyme [35]. Only 70% of women are active metabolizers of TAM, while the others are intermediate or poor metabolizers. Patients carrying the variants of CYP2D6 alleles and treated with TAM have significantly more breast cancer recurrences, shorter relapse-free periods (HR =2.24, p=0.02), and worse event-free survival rates (HR= 1.89; p=0.02), compared with the wild type carriers [36]. A very interesting modeling study, compiling the annual risk of recurrence derived from the BIG 1-98 trial, the genotype frequencies and the HR for cancer recurrence on TAM, showed that the 5-year DFS for patients treated with TAM and no CYP2D6 mutations (wt/wt) was 83.9%, i.e. essentially the same as 84.0% for genotypically unselected patients treated with letrozole. Based on these figures, the authors recommend this type of intervention in order to select patients for a specific adjuvant hormonal treatment [37].

Finally, it is worth stressing that a definitive conclusion regarding an optimal alternative for the use of adjuvant AI in ER+postmenopausal women is unlikely to be recommended. The final results of the BIG 1-98 trial, comparing all 4 treatment arms, are eagerly awaited. However, the following hints, based on the available data could be used to guide our clinical decisions: a) comparing with TAM, the upfront administration of AI improves the DFS but not the OS; b) the patients included in the upfront AI trials are undertreated with respect to CT; c) the confounding impact of CT should be considered while evaluating the adjuvant hormonal treatment trials; d) the sequential use of AI after TAM reduces DFS and OS; e) the trials using the switch strategy do not take into consideration the early relapse period; and f) where available, the genomic tests could be used to guide the most appropriate adjuvant strategy for ER+, postmenopausal patients.

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