REVIEW

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Adjuvant endocrine therapies for premenopausal women

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Abstract Adjuvant endocrine treatment for premenopausal woman remains a controversial area in the therapeutical approach of early stages of breast cancer. Meta-analysis show that ovarian ablation and suppression produce, in a global way, significant benefits in terms of reduction of the risk of recurrence and death. Nevertheless, in the presence of adjuvant chemotherapy, the benefits of ovarian suppression or ablation are clearly reduced, probably in relation to the impact that amenorrhoea induced by chemotherapy. On the other hand, in premenopausal patients, the same metaanalysis show that the use of adjuvant tamoxifen produces benefits in disease-free survival and overall survival very similar to those observed in postmenopausal women. Additionally, the benefits from tamoxifen persist independently of whether or not adjuvant chemotherapy is being received. Thus, some of the questions to answer are: first, is there, in premenopausal women, an additional benefit when ovarian suppression is associated to tamoxifen? Second, it remains controversial if ovarian suppression must be indicated for all patients who receive chemotherapy or only those that have not reached amenorrhoea when adjuvant chemotherapy is completed. Moreover, although in the last decades more than 15,000 premenopausal patients have been included in specific trials of adjuvant endocrine therapy with ovarian suppression or ablation, the best modality of treatment has not been established, and what is more important, the role of its association with tamoxifen has not been completely defined. Many of these aspects remain controversial and the decision about the best therapeutical approach must be individualised in each patient.

Key words Breast cancer • Adjuvant therapy • Premenopausal

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Introduction

Adjuvant endocrine treatment for premenopausal woman remains a specially complex and controversial area in the therapeutical approach of early stages of breast cancer. Adjuvant chemotherapy is administered in a high proportion of patients and it often causes ovarian dysfunction. This is, among others, one of the main factors that makes the interpretation of the results of the trials and metaanalysis in this population difficult; discerning the contribution that individual treatments have made to the final benefit is frequently complicated.

Moreover, although in the last decades more than 15,000 premenopausal patients have been included in specific trials of adjuvant endocrine therapy with ovarian suppression or ablation, the best modality of treatment has not been established, and what is more important, the role of its association with tamoxifen has not been completely defined.

In the last years, advances in the adjuvant endocrine therapy of breast cancer have been specially relevant in postmenopausal women, whereas the importance of endocrine treatment in premenopausal women is frequently underestimated. However, in Spain, approximately one third of breast cancer patients are premenopausal [1]. If we consider that about 75% of breast tumours show positivity for oestrogen/progesterone receptors [2], we see that the decision about the best adjuvant endocrine therapy in premenopausal women is performed frequently. Due to this, we will dedicate the present review to analysing this topic.

Modalities of endocrine therapy in premenopausal women

Ovarian ablation (oophorectomy and ovarian irradiation)

The first endocrine treatment for breast cancer was at the end of the 19th century when Beatson communicated the efficacy of oophorectomy as a treatment for patients with

metastatic breast cancer [3]. Oophorectomy can be performed by surgery or radiotherapy techniques with comparable efficacy. The development of the LHRH analogues, which induce a chemical castration, has led to the cessation of these modalities of treatment. Other surgical procedures like adrenal gland or hypophysis resection fell into disuse because of the development of less aggressive procedures with fewer adverse effects.

Luteinising hormone–releasing hormone (LHRH) analogues

LHRH analogues are peptides with activity 50–100 times superior to the endogenous hormone. They produce an initial stimulus of the production of luteinising hormone (LH) and follicle-stimulating hormone (FSH) on the hypophysis. Later they induce a severe suppression of the hypothalamus–hypophysis axis. Goserelin, buserelin, triptorelin and leuprolide are the most commonly used in clinical practice.

Selective oestrogen receptor modulators (SERMs)

The main drug of this group is tamoxifen. Its mechanism of action is based in its union with the intracytoplasmic oestrogen receptor (ER). The complex tamoxifen receptor binds to DNA, partially blocking transcription and thus tumour growth.

Aromatase inhibitors

Frequently used in postmenopausal women, their administration in premenopausal patients remains restricted to clinical trials that evaluate its activity associated with ovarian suppression with LHRH analogues. At present, there is no information that allows clinicians to recommend this association in clinical standard practice. They block the source of oestrogens that come from the transformation of the adrenal androgens to estrone and estradiol by the aromatase.

Metaanalysis of adjuvant endocrine therapy in premenopausal women

The information of the last update of the metaanalysis of the EBCTCG published in 2005 shows that ovarian ablation (surgery or radiotherapy) and ovarian suppression (LHRH analogues) in premenopausal women produce, in a global way, significant benefits in terms of reduction of the risk of recurrence and death [4].

Nevertheless, in the presence of adjuvant chemotherapy, the benefits of ovarian suppression or ablation are clearly reduced, probably in relation to the impact that amenorrhoea induced by chemotherapy has in this patients, as has been commented on previously. The interpretation of the metaanalysis in this population of patients is limited, even more so if we consider the frequent incorporation in this trials of women with unknown or negative ERs and the heterogeneity of the design of the studies (presence/absence of chemotherapy, presence/absence of tamoxifen, duration of the treatment, different drugs and procedures for castration, etc.).

On the other hand, in premenopausal patients, the same metaanalysis shows that the use of adjuvant tamoxifen produces benefits in disease-free survival (DFS) and overall survival (OS) very similar to those observed in postmenopausal women. Additionally, the benefits from tamoxifen persist independently of whether or not adjuvant chemotherapy is being received. This information and other data from trials like the IBCSG 13-93 study [5] – in which the addition of tamoxifen to adjuvant chemotherapy adds significant benefit – and the INT 0101 study [6] – which will be mentioned later in this review – lead to the consideration of treatment with tamoxifen in the adjuvant setting in all patients with hormonal positive receptors, independent from the association or not with ovarian suppression.

Thus, some of the questions to answer are: first, is there, in premenopausal women, an additional benefit when ovarian suppression is associated to tamoxifen? Second, it remains controversial if ovarian suppression must be indicated for all patients who receive chemotherapy or only those that have not reached amenorrhoea when adjuvant chemotherapy is completed.

Ovarian suppression/ablation *vs.* chemotherapy (Table 1)

Data from five randomised studies with this design are available. The main trial of these groups is the ZEBRA study, which compared, in 1640 patients, the administration of goserelin for two years *vs.* 6 cycles of adjuvant chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (FU) (CMF) [7]. In patients with positive ER, both treatments showed similar results, whereas, as expected, CMF was superior in patients with negative ER.

Moreover, the benefit achieved with CMF was higher when patients were amenorrhoeic after chemotherapy.

As a whole, the analysis of five of the trials allows us to conclude that adjuvant endocrine therapy with ovarian ablation or suppression (in the absence of chemotherapy and tamoxifen) proves to be at least as effective as CMF in premenopausal patients (global differences are not reached in DFS or OS in any of the trials). However, it is necessary to consider that nowadays most of these patients receive adjuvant chemotherapy

Table 1 Ovarian suppression/ablation *vs.* chemotherapy

Trial	Char. pat.	Treatment	FU (y)	DFS	OS	
ZEBRA *EJC '03*	1640 pt N+ 80% ER+	CMF×6 *vs.* goserelin×2a	6	NS	NS	No differences in global analysis CMF better in ER neg CMF and amenorrhoea: better
Scottish *Lancet '93*	332 pt N+ N–	OA CMF×6–8	10.7	NS	NS	–
Escandinav. *ASCO '99*	732 pt N+ N–	OA CMF×9	5.7	NS	NS	–
GAVG-A-93 *ASCO '04*	771 pt N–	CMF×3 *vs.* goserelin×2 a	4.9	NS	–	–
Wallwiener *ASCO '04*	599 pt	CMF×6 Leucoprolide+2 y	3	NS	NS	

CMF, cyclophosphamide, methotrexate, 5-fluorouracil; *DFS*, disease-free survival; *NS*, not significant; *OA*, ovarian ablation; *OS*, overall survival

and therefore the question of the benefit of ovarian ablation/suppression after chemotherapy is not answered. On the other hand, none of the trials of this group includes in its design treatment with adjuvant tamoxifen, which is clearly useful in the adjuvant setting, as has been previously mentioned [7–11].

Ovarian suppression/ablation plus tamoxifen *vs.* chemotherapy (Table 2)

Three of four studies published with this design do not show differences in efficiency among the arms of treatment [12–15]. Only the ABCSG-5 trial shows advantages in 5-year DFS in favour of the group of combined endocrine treatment compared to chemotherapy with CMF [12].

Thus, as a whole, the adjuvant ovarian ablation/suppression associated to tamoxifen (in absence of chemotherapy) proves to be at least as effective as chemotherapy (CMF or FAC or FE50C) in premenopausal women, but again it is necessary to remember that at present, most of these patients receive adjuvant chemotherapy and therefore once again the question of the additional benefit of this approach is not answered.

It must also be considered that with the design of these studies, again, none of them allow us to know if the results are attributable to the ovarian suppression or to the well known effectiveness of tamoxifen.

Ovarian suppression/ablation after chemotherapy (Table 3)

The first one of the studies published, the IBCSG-VIII, was conducted in more than 1000 premenopausal women without axillary involvement. The design included three arms of treatment: adjuvant chemotherapy with six cycles of CMF *vs.* goserelin for 2 years *vs.* CMF followed by goserelin [16]. Only 68% of the pa-

Table 2 Ovarian suppression/ablation+tamoxifen *vs.* chemotherapy

Trial	Char. pat.	Treatment	FU	DFS	OS	
ABCSG-5 *JCO '02*	1045 pt N+ ER+ 50%	CMF×6 *vs.* goserelin×3+Tam×5	5 y	76% *vs.* 81% (5 y DFS) p=0.037	NS	
GROCTA *JCO '00*	244 pt N+ 91% ER+ 86%	CMF×6 OA+Tam ×5	76 m	NS	NS	
FASG 06 *ASCO '00*	333 pt N+	FE50C×6 *vs.* triptorelin+Tam×3	54 m	NS	NS	
French Trial *ASCO '96*	162 pt N+	CAF×6 *vs.* OA+Tam×2	84 m	NS	NS	Early closed

Table 3 Ovarian suppression/ablation after chemotherapy

Trial	Char. pat.	Treatment	FU (y)	DFS	OS
IBCSG-VIII *JCO '02*	1063 pt N0 HR+ 68%	CMF×6 *vs.* goserelin×2 y CMF×6→Goser×2 y	7	NS	NS
Arriagada *Ann Onc '05*	926 pt N+ 90% HR +80%	QT*×6 *vs.* QT[a]×6→OS[b]	9.5	NS	NS
INT 0101 *JCO '05*	1503 pt N+ HR+	CAF×6 *vs.* CAF×6→Goser CAF×6→Goser+Tam	9.6	CAF *vs.* CAF-Z NS CAF-Z *vs.* CAF-ZT HR 0.74 $p<0.01$	NS

[a]Anthrac. 2/3 pac
[b]RT or Triptorel×3

tients included had ER-positive tumours. There were no differences in DFS or OS in the global analysis. Superiority existed in DFS for the arm of CMF followed by goserelin in the subgroup of younger patients (less than 40 years old) with positive ER. This can be related to the fact that fewer of this group of patients reaches amenorrhoea induced by chemotherapy.

Another published trial, updated in 2005, reinforces these results [17]. A total of 926 patients were randomised to receive adjuvant chemotherapy (anthracycline-based in 2/3 of the cases) followed or not by ovarian suppression or ablation (with radiotherapy or triptorelin). ER were positive in 80% of the patients. Once again, differences did not exist in DFS and OS in the whole group and, again, superiority existed in DFS for chemotherapy followed by suppression in the subgroup of patients younger than 40 and with positive ER.

After the analysis of the results of these two trials it is possible to conclude that, although globally adjuvant endocrine therapy with ovarian ablation or suppression after chemotherapy does not contribute significantly to improve the results in all the patients, there are subgroups of patients who benefit, essentially those who do not reach amenorrhoea induced by chemotherapy. Nevertheless, again, tamoxifen was not administered in any of these studies, and this fact limits the interpretation of the results.

For this reason (the absence of tamoxifen in any of the arms of treatment of the previous studies), the information obtained from the recently published INT 0101 (E5188) trial [6] is of special interest. In this study, 1503 premenopausal women with node-positive breast cancer and positive ERs were randomised to receive six courses of chemotherapy alone (CAF regimen) *vs*. CAF followed by two years of goserelin (CAF-Z) *vs*. CAF-Z plus adjuvant tamoxifen for 5 years (CAF-ZT). There were no differences between CAF and CAFZ, whereas CAF-ZT was superior to CAF in the reduction of the risk of recurrence and in time to recurrence. Therefore, this trial suggested that the benefit of the hormonal treatment came from the addition of administration of tamoxifen or, put differently, ovarian suppression after chemotherapy and in the absence of tamoxifen does not contribute with significant benefits to the whole group of hormonal-sensitive tumours in premenopausal women.

More information – or even more doubts – in this regard is obtained from the ZIPP trial, recently published in its entirety. The ZIPP trial, with 4 arms of treatment, is really the joint analysis of 4 studies with similar design [18]. It compares, after a "standard treatment" of the participant centres, (a) no adjuvant endocrine therapy, (b) adjuvant goserelin, (c) adjuvant tamoxifen and (d) adjuvant goserelin plus tamoxifen. Duration of treatment with tamoxifen was clearly suboptimal, as it was only maintained for 2 years (the same time as goserelin). A total of 2641 patients were included, 42% with positive axillary nodes and only 60% with positive ER. In addition to all the problems of design enumerated previously, it is necessary to consider two significant facts that question the analysis of the study. The first one is the fact that treatment with tamoxifen was allowed for every centre to be random or elective (which constitutes an unquestionable bias) and, secondly, the administration or not of chemotherapy was based on the criteria of every clinician (only 43% of the patients received it). Regarding the results of the trial, goserelin improved the DFS and OS compared with no goserelin (specially for patients over 40 years old (RR=0.75; 95% CI 0.63–0.89). There was no benefit for goserelin plus tamoxifen *vs*. tamoxifen alone. The benefits were only significant for patients without chemotherapy (RR=0.69; 95% CI 0.56–0.85). Additionally, tamoxifen alone *vs*. no tamoxifen also offered a significant benefit. Once again, in the presence of chemotherapy, ovarian suppression seems to have a limited role (Table 4).

The results of the National Cancer Institute of Canada Clinical Trials Group Study – NCIC CTG MA.5 trial [19], and the IBCSG 13-93 trial [5], which conclude

Table 4 Ovarian suppression/ablation after chemotherapy. The ZIPP Trial

ZIPP Trial *EJC 2006*	Standard treatment Standard treatment+goserelin 2 y Standard treatment+tamoxifen 2 y Standard treatment+goserelin 2 y tamoxifen 2 y
N=2631 (combined analysis of 4 trials with a similar design) N+, 42% ; ER+, 60% Random or elective tamoxifen treatment Chemotherapy based on investigators criteria (43% of patients) Tamoxifen only 2 years	
	Goserelin improves DFS or OS compared with no goserelin Greater benefit in >40 y (RR=0.75; 95% CI 0.63–0.89) No benefit for goserelin+tamoxifen *vs.* tamoxifen alone Benefit only for patients without chemotherapy (RR=0.69; 95% CI 0.56–0.85) Tamoxifen alone *vs.* no tamoxifen also reach significant benefit

that the absence of amenorrhoea induced by chemotherapy leads to a worse outcome in patients treated with adjuvant chemotherapy, can continue supporting the strategy of administering adjuvant LHRH analogues to those premenopausal patients that do not receive adjuvant chemotherapy or those that continue menstruating after it. Nevertheless, on the basis of the existing evidence, ovarian suppression must be considered always to be associated with tamoxifen.

Ongoing trials

Diverse ongoing trials evaluate the role of adjuvant endocrine treatment in premenopausal women. Some of them include, as a common feature, in association with ovarian suppression, once pharmacological castration is achieved, the incorporation of an aromatase inhibitor.

The TEXT trial compares LHRH analogues plus tamoxifen for 5 years *vs*. LHRH analogues plus exemestane for 5 years. The inclusion criteria allow the inclusion of patients with or without adjuvant chemotherapy.

The SOFT trial is of special interest because patients are included only if they persist without amenorrhoea (those not receiving adjuvant chemotherapy or those that in spite of receiving it continue with normal ovarian function) and one of the arms of the study includes treatment with tamoxifen alone *vs*. ovarian ablation/suppression plus tamoxifen *vs*. ovarian ablation/suppression plus exemestane. This design will allow the questions raised at the beginning of this review to be answered.

Conclusions

Without doubt, adjuvant endocrine treatment in premenopausal women with breast cancer and positive ERs has been shown in the last decades to reduce recurrence and improve the survival rates, independently of the benefit obtained with other systemic treatments.

Adjuvant tamoxifen achieves comparable benefits to those obtained in postmenopausal women. Data from metaanalysis show that ovarian suppression – without tamoxifen – diminishes the risk of recurrence and increases the survival of the global population of premenopausal patients, although the benefit is obtained essentially in the patients who do not receive adjuvant chemotherapy. There is no evidence to recommend ovarian suppression in patients with amenorrhoea induced by chemotherapy. Thus, after chemotherapy, LHRH analogues can be considered in patients without amenorrhoea, in association with tamoxifen.

Nevertheless, many of these aspects remain controversial and the decision about the best therapeutical approach must be individualised in each patient.

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