Neoadyuvant Hormonotherpy for Posmenopausics Women with Locallity Advanced Breast Cancer

Novoa Vargas Arturo*

Oncology Surgeon, Tuxpan No. 29, 5º piso, Consultorio 516, Col. Roma Sur. CP: 06760, México City, México

Abstract: Objective: Present display the objective respond, frequency complete clinical response and pathological complete response with the use of induction hormonotherapy in posmenopausic women with locally advanced breast cancer, (stages III).

Methods: Analysis in a Regional General Hospital of a State of Mexico, Mexico; 80 patients with chanalicular infiltrate breast cancer. Positive hormonal receptors: estrogen and progesterone, inmunohistochemical study with Her2 and p53. Eligible's patients were treated in a prospective study, to double blind, using *per os*: letrozol, 2.5 mg; exemestan, 25 mg and anastrozol, 1 mg with aromatase inhibitors; tamoxifen, 20 mg; during 36 consecutive months. Reports were taken at the beginning, subsequent to 3 months and 6 months ago to evaluate the frequency of objective respond. Patients, whom did not show response to neoadjuvant therapy, became treatment with radiotherapy. Patients, whom showed complete or partial clinical respond, went candidates to radical mastectomy. It was used statistical method Chi 2, with *p* of Mantel-Haenzel table to evaluate differences.

Results: During a period of 3 years, january of the 2006 to january of the 2009, 4 groups of patients, 80 studied altogether; the age average was 66.5 years old, with a rank of 45 to 75 years with breast cancer, stages IIIA to IIIB, FIGO stages. Objective respond, OR=55%, 44 patients; Clinical respond, 32 patients (40%); ClR plus CPR, complete pathological respond, 12 patients (15%), *p=0.05;* Complete pathological respond was founded in 12 patients (15%); 40% with aromatase inhibitors and with tamoxifén TMX, 15%, *p=0.05*. Without Clinical respond (<50% tumoral volume) in eleven patients: 5 patients; 25% in tamoxifen group and 19% in patients with aromatase inhibitors group, *p=0.05*. These patients over express the proteins HER2/neu and p53 were positive. Collateral effects used NA hormonotherapy with aromatase inhibitors was 23% and with the use of tamoxifen in 32% of the patients, *p = 0.05*. They didn't respond to neoadyuvant therapy with hormonal receptors <30%, 19% aromatase inhibitors patients; with anastrozol, 10%; with exemastane, 5%; with letrozol, 4% and 25% with tamoxifen; reason why, they received treatment with radiotherapy, because they didn't accept chemotherapy. All patients candidates to surgery were benefitted with the mastectomy surgery.

Conclusions: HTNA is a good therapeutic alternative in posmenopausic women with locally advanced breast cancer, whom didn't accept chemotherapy.

Work shows efficacy of the HTNA for identify patients with breast cancer and hormonal receptors positives, without over express the protein HER2 and p53, they have better survive prognosis and could be rescue with mastectomy.

It's a preliminary study shows there are significance difference in objective respond between aromatase inhibitors and tamoxifen treatments, used in NA form for patients with breast cancer stage III.

In future we will search objective respond between hormonotherapy and chemoterapy used in NA form, in posmenopausic patients.

Keywords: Breast cancer, neoadjuvant hormonotherapy.

INTRODUCTION

We have shown in previous studies that the aromatase inhibitors and tamoxifen are effective as drugs in postmenopausic women with locally advanced tumors stage III and in hormonal status [1, 2]. In the present study we researched the roll of best-known anti-estrogens, third generation aromatase inhibitors: exemestane, anastrozole and letrozole and compared with tamoxifen; all of them used as neoadjuvant therapy. Objective work is show a good alternative treatment in patients whom don't accept or is contraindicated the use of systemic chemotherapy, especially in old patients with chronic degenerative diseases. In Mexico, we are pioneer used neoadyuvant hormonotherapy NAHT in breast cancer, there is the antecedent of a previous NAHT work where we compared the utility of tamoxifen and letrozole, this latter, proved to be better in women with locally advanced postmenopausic breast cancer [3].

The report is a prospective study conducted in a Urban Government hospital, General-Regional Social Security Institute (IMSS) in women with breast cancer, infiltrating canalicular, locally advanced lineage, where the objective of the work was to demonstrate the goodness of hormone therapy used in the form of 'initial' or neoadjuvant, precisely in those postmenopausal women, positive hormone receptors, in locally advanced stages (stage III), without desire for systemic chemotherapy.

*Address corresponding to this author at the Oncology Surgeon, Tuxpan No. 29, 5º piso, Consultorio 516, Col. Roma Sur. CP: 06760, México City, México; Tel: (02 54)52-65-29-49; Fax: 55-16-95-13-55;
E-mail: novoaart@prodigy.net.mx

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SUBJECTS AND METHODS

In an Urban hospital General-Regional of the IMSS, upon acceptance by the local Committee of research and Ethics with signature of consent for receiving neoadjuvant hormone therapy, It was informed of the protocol to postmenopausic patients with a diagnosis of breast cancer, developed a prospective analysis in 80 patients with breast cancer in stage III. All patients with neoplasic infiltrating canalicular, hormonal receptors (HR) with positive estrogen and progesterone reports, Immunohistochemistry: HR more than 30%, and quantified: p53 protein, Her2, epidermal growth factor. A double-blind study, divided into 4 groups, each of one with 20 patients. Four drugs anti-estrogenic were used in three groups with third generation aromatase inhibitors: letrozole, anastrozole and exemestane; and tamoxifen, widely known as selective estrogen receptor modulator; all ministered *per os*, daily: 2.5 mg, 1 mg, 25 mg and 20 mg respectively, along 36 consecutive months. Reports were analyzed at the beginning, after 3 months and 6 months later to assess the frequency of clinical, pathological complete responses and objective responses. Patients, whom no response to neoadjuvant letrozole, anastrozole, exemestane, or tamoxifen therapy, were became treatment with radiotherapy, because they did not accept chemotherapy. Patients showed complete clinical response (CClR) or pathological complete response (PCR), were candidates for radical mastectomy.

According to the protocol of the study, the patients after surgery, whom showed partial or complete pathological response continued adjuvant treatment with letrozole, anastrozole and tamoxifen 2 consecutive years more or presence of disease progression.

Used as a statistical method Chi 2, with *P* of Mantel-Haenszel to evaluate differences.

RESULTS

4 groups were studied during a period of 3 years, January 2006 to January 2009, 80 in total; the average age was 65.5 years, with a range of 45 to 75 years with breast cancer, without pretreatment, in stages: IIIA and IIIB of the FIGO classification.

Complete Clinical Response (CClR)

Complete clinical response (CClR) was presented in 32 patients (40%), 15%, 25%, 29 women; and 3 patients with tamoxifén, patients with letrozole, exemestane and anastrozole: 8, 11 and 10 patients respectively, *p = 0. 05,* (Figure **1**).

Pathological Complete Response (PCR)

In total were 12 women (15%); patients with anastrozole, exemestane, and letrozole had RPc in 11% of them (11 patients); those in the tamoxifen group, only 1 woman (4%), *p = 0. 05,* (Figure **2**).

Response Objective (RO) = CClR + CPR

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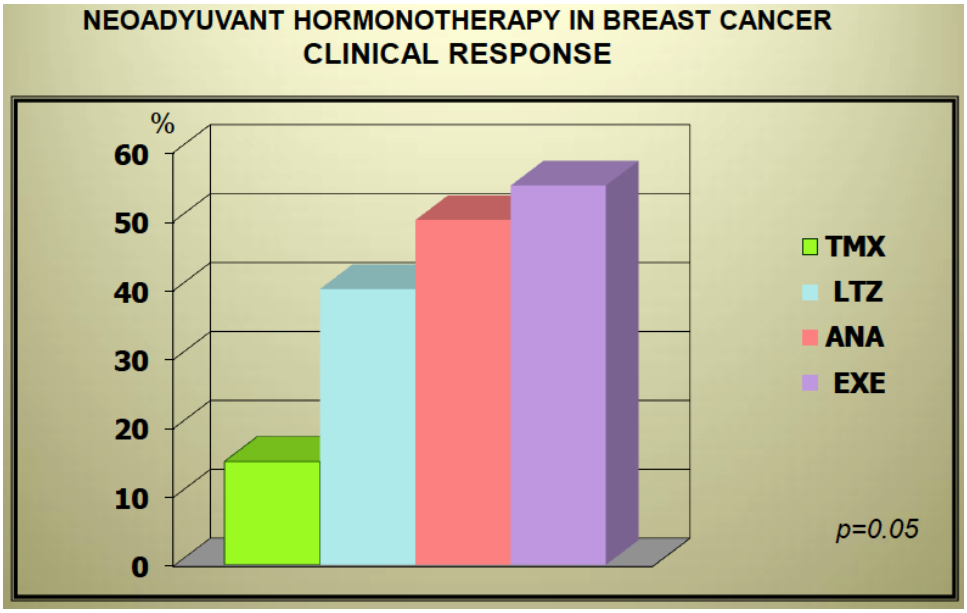

Figure 1: Clinical Response ClR- TMX 3 pts.(15%); LTZ 7 pts. (40%); ANA 9 pts. (50%), EXE 11 pts (55%).

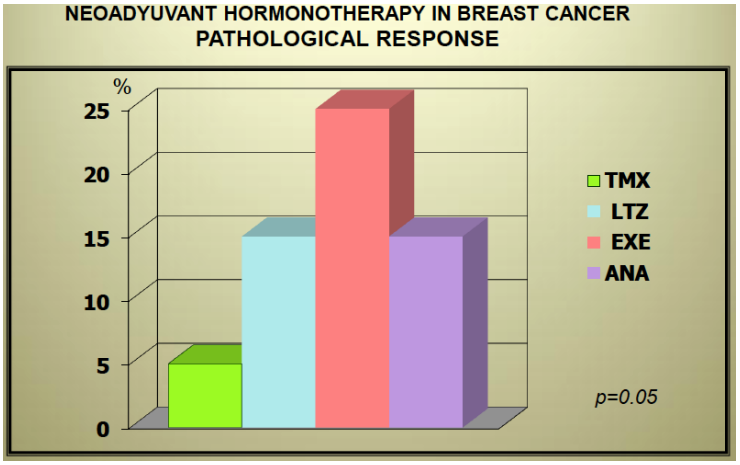

Figure 2: Pathological Response (PR).- TMX 1 pts.(5%); LTZ 2 pts. (15%); ANA 2 pts. (15%), EXE 5 pts (25%).

total were 44 patients (55%); with TMX, 4 patients (20%) and 40 women (35%); with aromatase inhibitors: letrozole, anastrozole and exemestane, *p = 0.05,* (Figure **3**,**4**).

Without Clinical Response

Without clinical response was 25% with tamoxifen and aromatase inhibitors 19%; 4% with letrozole; 5% with exemestane and 10% with anastrozole. In them,

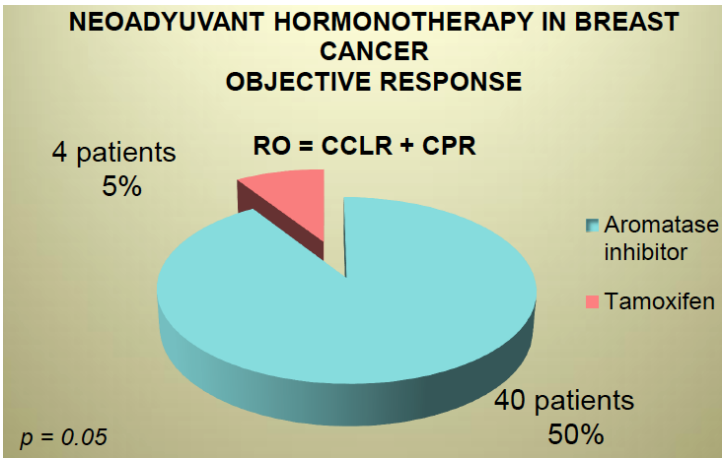

Figure 3: Objective response (OR) = Complete Clinical Response (CClR) + Complete Pathological Response (CPR).

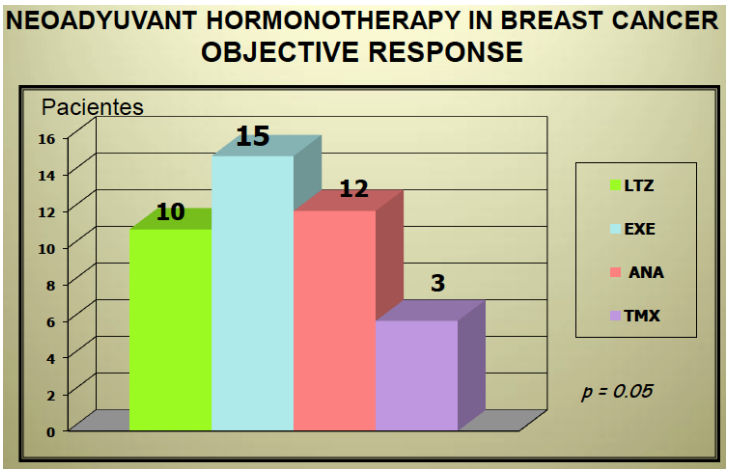

Figure 4: ObjeCtive Response (OR) = 40 patients: complete clinical response (LTZ)Letrozol; (EXE) Exemestan; (ANA) Anastrozol; (TMX) Tamoxifen.

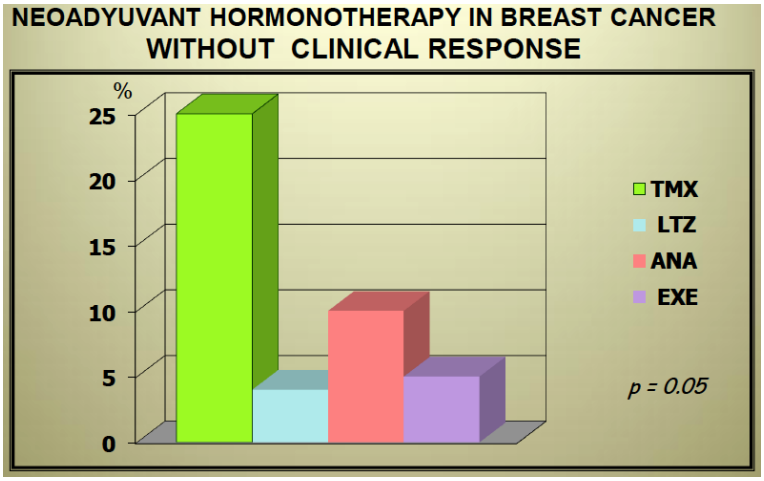

Figure 5: No Clinical Response (NoCR) Observed in 11% of the group; with tamoxifen (TMX) 25%; 5% with exemestan (EXE); anastrozol (ANA) 10% and patients with letrozol (LTZ) in 4%.

with poor response to the HTNA, RH results < 30% and of immuno-Histochemistry, with overexpression of the protein Her2 and the magnification of p53 also were positive (Figures **5**).

Side Effects

Side effects mild to moderate, were presented in 38 patients (47%); being the most common vasomotor phenomena and the exacerbation of peripheral venous insufficiency; with aromatase inhibitors in 26 patients, and with the use of tamoxifen in 12 patients (*p = 0.05*) were presented (Figure **6**).

Cases that non-responding HTNA and systemic chemotherapy accept received management with radiotherapy, complete breast cycle of 5,000 cGy. In all patients surgery candidates were benefited with the radical mastectomy.

DISCUSSION

The prognosis is associated with the stage of the disease, the degree of differentiation, the margins of resection, the levels of expression of estrogen-progesterone receptors and the age of the onset of the condition. Moreover studies of Immunohistochemistry as: Her2 (epidermal growth factor) and the p53 protein, play a primary role in the progression-free survival of women with breast cancer; because it's well known in the literature, useful adjuvant hormone therapy on them, either with anti-estrogens or with 3rd generation aromatase inhibitors and positive estrogen and progesterone receptors. The yield of the postmenopausic patients using orally anti-estrogens like tamoxifen as adjuvant, demonstrated over 50 years ago, its great benefit. Today, it's the standard adjuvant therapy for woman with breast cancer in postmenopausal status, independent of the stage [4].

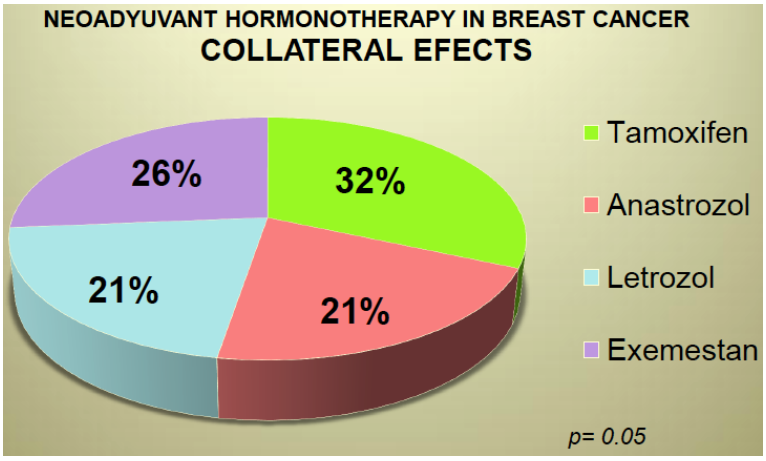

Figure 6: Collateral efects: Tamoxifen (TMX) 12 patients; Anastrozol (ANA) 8 paients; Letrozol (LTZ) 8 paients; Exemestan (EXE) 10 patients.

Clinical trials have demonstrated the benefit of neoadjuvant chemotherapy use, especially in patients with poor prognosis, as "triple negative" factors, premenopausal, with magnification of p53 and Her2 negative [5, 6].

In comparative form, we used the benefit of four drugs in neoadyuvant or induction form: an anti-estrogen modulator, worldwide known the most used in the field of handling hormone, as tamoxifen, and three of third generation aromatase inhibitors: letrozole, anastrozole and exemestane; in this work we used them in novel ways, neoadjuvant or induction form in patients didn't accept systemic chemotherapy.

The TAMOXIFEN. It is a selective modulator of estrogen receptors in breast tissue, is a competitive antagonist of the nuclear estrogen receptor; so the tamoxifen inhibits the activity mediated by estrogen, once it binds to the receptor, tamoxifen blocks the transcription and post transcriptional events. In bone, liver and endometrial tissue, the transcription of genes regulated by estrogen is unchanged; later, tamoxifen acts on these sites as an estrogen agonist [7]. Based on the results of the NSBP, National surgical breast project, the draft Prevention for breast cancer and the FDA, approved to the tamoxifen label "reduce the risk of breast cancer in women at high risk" [5]; high-risk was defined for breast cancer as "woman under 35 years of age with a predictable risk to 5 years for breast cancer > or = 1.67%, calculated using the Gail model", the ASCO, American Society of Clinical Oncology, recommended that tamoxifen used to 20 mg/day for more than 5 years, can provide women with an increased breast cancer risk, projected protection > or = 01.66% [8-10]. The preventative effects of tamoxifen are in relation to some important female characteristics, says Fisher *et al*., in their report: woman postmenopausal estrogen receptor positive, history of non-invasive breast cancer, both lobular in situ carcinoma (CLIS) and atypical hyperplasia [11]. Furthermore, as says Beattie *et al*., in the population of women at high risk for developing breast cancer, the levels of sex hormones, they are not associated with increased risk of breast cancer. Therefore, it concludes that endogenous plasma levels of estradiol or testosterone, are not helpful to identify women who may be benefited with tamoxifen. Women with elevated plasma estradiol concentrations or testosterone, had a reduction in risk similar with preventive tamoxifen treatment, similar to that which had low concentrations of hormones [12]. When adverse events were considered in Caucasian women, 10% or less, in all age groups were potentially elected for chemo-prevention. The ratio maximum prevention of breast cancer in women elected was 6.0% to 8.3% [13]. Tamoxifen is the most widely used agent as secondary prevention in women survivors of breast cancer, with a reduction of 50% in the recurrence of cancer. The agent is associated with proliferative effects on the endometrium, as well as increasing the frequency of venous thrombosis deep.

AROMATASE-INHIBITORS

They have had the greatest impact in the treatment of breast cancer. Especially in women where the gonads function has diminished or completed; be shaped by menopause natural or induced in artificial form (chemotherapy) or surgical. These aromatase inhibitors canceled the aromatization of the P450 enzyme which catalyzes the conversion of androgens into estrogen in the "peripheral tissues", such as fat, liver, breast and muscle cells [14] and in the tumor tissue of the breast; If only, reduces the synthesis and the expense of estrogens in postmenopausal women. Third generation aromatase inhibitors include: agents non-steroidal as anastrozol and letrozole and a compound I steroid called exemastano, have proved to be better than the tamoxifen for post-menopausal women, estrogen hormone receptors and with high risk for breast cancer. In our study used in NA form, they also proved to be better than the TMX. The IBIS-II (International Breast Intervention Study II), large study randomized, multicenter study, double-blind; study controlled in female postmenopausal with ductal carcinoma in Situ (DCIS), in charge of investigating which of the two is best results between anastrozole and tamoxifen, being the top 1st, results from the ATAC study (anastrozole and tamoxifen alone or in combination): healthy women at high risk for breast cancer, received anastrozole (1 mg/day) or placebo for 5 years; While patients with proven total resection of ductal carcinoma in situ, received anastrozole (1 mg/day) or tamoxifen (20 mg per day) for 5 years. This comparison is justified by the results of the study NSABP B-24, which showed tamoxifen reduced the frequency of cancer cases of subsequent breast after Lumpectomy for ductal carcinoma in situ [15]. Indicated shaped adjuvant Aromatase inhibitors showed significant reduction in breast cancer against side compared with tamoxifen or placebo [16]. In premenopausal women, tamoxifen induces increased levels of estradiol, 3000 pmol/l or more, thereby reducing the occupation of the RE per le tamoxifen and its metabolites. This increase is prevented with GnRH

agonists, which can participates superiority observed in combination with advanced disease [17]. In postmenopausal women, occupies 99.9% of estrogen receptors. Its estrogenic agonist effect can be dominant as when tamoxifen is present with an inhibitor of aromatase [18].

At the current time, the most important benefit of neoadyuvant therapy is its “adyuvant” effect on long-term recurrence and mortality.

CONCLUSIONS

- Induction or neoadjuvant (HTNA) hormone therapy in postmenopausal patients with locally advanced breast cancer is a good therapeutic alternative for those who do not accept chemotherapy.
- The study demonstrated the effectiveness of the HTNA to identify those sick with breast cancer with positive hormone receptors and Her2 and p53, have better prognosis to be rescued with mastectomy.
- Preliminary study that proved to be significant difference in the objective response between different the tamoxifen and aromatase inhibitors used in neoadjuvant form for patients with stage III breast cancer.
- In the near future we will investigate objective responses comparing postmenopausal patients with breast cancer, locally advanced with RH, Her2 and p53 positive, using chemotherapy and hormone therapy in a way NA.

REFERENCES

[1] Forbes JF. The control of breast cancer: the role of tamoxifen. Semin Oncol 1997; 24(Suppl 1): SI-5-19.

[2] Ellis MJ, Coop A, Singh B, *et al*. Letrozole is more effective neoadyuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor - positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol 2001; 19: 3808-16.

[3] Novoa VA. Letrozole compared with tamoxifen as neoadjuvant therapy for locally advanced, in patients postmenopausal hormone-dependent breast cancer. GAMO 2010; 9(2): 12-17.

[4] Put them TJ. Efficacy of tamoxifen as treatment of breast cancer. Semin Oncol 1997; 24(Suppl 1): Yes-48-54.

[5] Tripathy D. Using neoadyuvant yherapy for breas cancer in clinical practice: when and how? Breast Cancer Res Treat 2012; 132: 775-77. http://dx.doi.org/10.1007/s10549-012-2030-8

[6] Liu SV, Melstrom L, Yao K, *et al*. Neoadyuvant therapy for breast cancer. J Surg Oncol 2010; 101: 283-91. http://dx.doi.org/10.1002/jso.21446

[7] Howell A. Antiestrogens: future prospects. Oncology 1997; 112(Suppl 1): 59-64.

[8] Litherland S, Jackson IM. Antioestrogens in the management of hormone-dependent cancer. Cancer Treat Rev 1988; 15: 183-94. http://dx.doi.org/10.1016/0305-7372(88)90002-3

[9] Put them TJ. Efficacy of tamoxifen as treatment of breast cancer. Semin Oncol 1997; 24(Suppl 1): Yes-48-54.

[10] Chlebowski RT, necklace, Somerfield MR et to the. American Society of Clinical Oncology technology assessment on breast cancer risk reduction strategies: tamoxifen and raloxifene. J Clin Oncol 1999; 17: 1939-55.

[11] Fisher B, Constantino JP, Wicheham DL, Cecchini RS, *et al*. Tamoxifen for the prevention of breast cancer: Current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 2005; 97: 1652-62. http://dx.doi.org/10.1093/jnci/dji372

[12] Beattie MS, Constantino JP, Cummings SR, Wickehman DL, *et al*. Endogenous sex hormones, breast cancer risk, and tamoxifen response: an ancillary study in the NSABP breast cancer prevention Trial (P-1). J Natl Cancer Inst 2006; 98: 110-15. http://dx.doi.org/10.1093/jnci/djj011

[13] Lewis CI, Kinsinger LS, Russell P, Harris MP, *et al*. Breast cancer risk in primary care. Implications for chemoprevention. Arch Intern Med 2004; 164: 1897-903. http://dx.doi.org/10.1001/archinte.164.17.1897

[14] Tobias JS. Recent advances in endocrine therapy for postmenopausal women with early breast cancer: Implications for treatment and prevention. Ann Oncol 2004; 15: 1738-47. http://dx.doi.org/10.1093/annonc/mdh485

[15] Cuzick J. Aromatase inhibitors in prevention-data from the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial and the design of IBIS-II (the second International Breast Cancer Intervention Study). Recent Results Cancer Res 2003; 163: 96-103, 264-266. http://dx.doi.org/10.1007/978-3-642-55647-0_9

[16] Goss PE, Strasser-Weippl K. Prevention strategies with aromatase inhibitors. Clin Cancer Res 2004; 10: 372-79. http://dx.doi.org/10.1158/1078-0432.CCR-031210

[17] Klijn JG, Morlock RW, Boccardo F, *et al*. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist along in premenopausal advanced breast cancer: a metaanalysis of four randomised trials. Cl J Oncol 2001; 19: 343-53.

[18] Dowsett M. the biology of steroid hormones and endocrine therapies. Breast 2005; 14(Suppl): S5. http://dx.doi.org/10.1016/S0960-9776(05)80010-4

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