Journal of Breast Cancer

J Breast Cancer 2010 September; 13(3): 242-9 DOI: 10.4048/jbc.2010.13.3.242

REVIEW ARTICLE

Adjuvant Hormonal Therapy: Current Standard and Practical Issues

Byeong-Woo Park, Hyung Seok Park

Department of Surgery, Yonsei University College of Medicine, Seoul, Korea

Adjuvant hormonal therapy is used as the first target-specific approach in curing breast cancers due to its high efficacy and mild side effects. Five years of tamoxifen therapy has been the gold standard for women with estrogen receptor-positive breast cancer irrespective of age or menopausal and nodal status. After the emergence of 3rd generation aromatase inhibitors (AI), the use of either tamoxifen or tamoxifen plus ovarian function suppression for 5 years has been proposed as an acceptable standard for premenopausal women while AI should form part of standard endocrine therapy for the postmenopausal women as established at the St. Gallen Concensus Conference. The addition of luteinizing-hormone-releasing hormone (LHRH) analogs might be beneficial for the younger patients who remain premenopausal after chemotherapy, however controversies over the addition of LHRH analogs remains. Further, it has been suggested that CYP2D6 polymorphisms and concomitant use of CYP2D6 inhibitors which reduce CYP2D6 activity may influence the clinical outcomes of adjuvant tamoxifen therapy. The androgen receptor has been evaluated as a prognostic or predictive marker for endocrine responsiveness in a few studies; however, there are many issues to be answered and ongoing clinical trials will provide the answers. Until then, it would be important for clinicians to carefully evaluate the risk factors of patients, monitor the compliance of those patients who are under endocrine therapy, and take care in selecting antidepressants when coprescription with tamoxifen is necessary. In the future, tailored therapy will be designed based on the target molecular profiling of the tumors, pharmacogenomics, and improved understanding of receptor signaling biology. More attention should be given to explore molecular markers that could differentiate the subsets for tailoring.

Key Words: *Aromatase inhibitors, Breast Neoplasms, Hormonal antineoplastic agents, Tamoxifen*

INTRODUCTION

Breast cancer has become the most common female cancer in many Asian and western developed countries. The incidence of early-stage breast cancer is steadily increasing and the risk of disease recurrence remains. Risk evaluation and selection of adequate adjuvant treatments are essential to reduce such recurrences. Because most estrogen receptor (ER)-positive breast cancers are dependent on estrogen for growth, ER-positive cancers have been the target of adjuvant endocrine treatment. Current primary strategies of adjuvant endocrine therapy are inhibition of estrogen synthesis and ER antagonists that block or destroy the ER.

Adjuvant hormonal therapy is the first target-specific approach for curing breast cancers due to its high efficacy and mild side effects. Five years of tamoxifen therapy has been the gold standard for women with ER-positive breast cancer irrespective of age or menopausal and nodal status.*(1)* However, its use has been challenged by the emergence of 3rd generation aromatase inhibitors (AI). At the St. Gallen Concensus Conference, five years of either tamoxifen or tamoxifen plus ovarian function suppression were proposed as acceptable standards for premenopausal women while AIs were suggested as part of standard endocrine therapy for the postmenopausal women.*(2)*

In order to maximize the efficacy and to minimize the side effects of adjuvant hormonal therapy, it is important to provide more detailed, improved, and individualized therapeutic strategies. Therefore, in the current paper,

Correspondence: Byeong-Woo Park
Department of Surgery, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea
Tel: 02-2228-2100, Fax: 02-313-8289
E-mail: bwpark@yuhs.ac
Received: July 14, 2010 Accepted: September 2, 2010

we have reviewed current standard and practical issues.

ADJUVANT HORMONAL THERAPY FOR THE POSTMENOPAUSAL BREAST CANCERS

Adjuvant hormonal therapy for postmenopausal breast cancers is relatively simple. Tamoxifen, which targets ER and AI which inhibit peripheral estrogen synthesis are the two main therapeutic agents. Issues for postmenopausal hormonal therapy involve whether to use AI, optimal timing and duration of AI, and which AI is the most effective.

Tamoxifen or aromatase inhibitors

Although 5 yr of adjuvant tamoxifen therapy was shown to significantly reduce the relative risk of recurrence by 41% and mortality by 34%,*(1)* 3rd generation AI showed superiority over tamoxifen in terms of disease-free survival (DFS) in various clinical trials such as those examining upfront adjuvant use,*(3,4)* switch adjuvant setting,*(5, 6)* and extended adjuvant therapy.*(7)* However, only switching to the use of anastrozole showed a significant benefit in overall survival (OS) in a subsequent meta-analysis.*(8)* Although a meta-analysis of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) and Breast International Group (BIG) 1-98 up-front use of AI studies revealed improved DFS but no significant difference in ovarian function suppression relative to tamoxifen,*(9)* the adjuvant use of AI reached consensus and became the standard of adjuvant hormonal therapy for the postmenopausal breast cancers except for in those patients who are contraindicated to AI use or are of very low risk of recurrence.

Despite this standard, remaining issues such as timing and duration of AI use, and the best AI to use did not reach consensus.

Timing of aromatase inhibitors

Since three different approaches such as upfront use, switching, and extended use of AI demonstrated the superior efficacy of AI over tamoxifen or placebo, The National Comprehensive Cancer Network (NCCN) guidelines recommended all three approaches.*(10)*

Both the BIG 1-98*(3)* and ATAC*(4)* studies reported improved DFS and time to distant recurrence in favor of AI with no impact on OS. A meta-analysis of the BIG 1-98 and ATAC upfront studies also demonstrated that AI reduced distant recurrence (hazard ratio [HR], 0.84; p=0.009), with no significant improvement over tamoxifen on OS.*(9)* The BIG 1-98 study revealed a nonsignificant difference between letrozole montherapy and tamoxifen monotherapy with respect to OS (p=0.08), a result which underestimates the survival benefit that would have accrued if there had been no crossover to letrozole.*(11)*

Although the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 8 trial (sequential use of AI)*(9,12)* did not show significant difference, a meta-analysis of switch studies including Arimidex-Nolvadex 95 (ARNO 95) trial, the Italian Tamoxifen Arimidex (ITA) trial, the Intergroup Exemestane Study (IES), and ABCSG-8 trial showed that AI significantly improved both distant recurrence (HR, 0.76; p=0.01) and breast cancer mortality (p= 0.02).*(9)*

To compare the upfront and sequential use of AI, BIG 1-98 data was analyzed at a median follow-up of 71 months,*(11,13)* Results demonstrated that there was no statistically significant difference in DFS between five years of treatment with letrozole versus the letrozole followed by a tamoxifen sequence versus the tamoxifen followed by a letrozole sequence. There was a nonsignificant increase in the risk of early relapse among women with node-positive disease who were assigned to tamoxifen followed by letrozole and upfront letrozole for two years followed by tamoxifen, yielding outcomes similar to those seen with letrozole monotherapy.*(11)*

The National Cancer Institute of Canada Clinical Trials Group MA.17 (MA.17) study randomized patients to receive either five years of letrozole or placebo after completion of five years of tamoxifen.*(7)* The trial was prematurely unblended at 2.4 yr of follow-up because letrozole significantly improved DFS and OS compared with placebo. The MA.17 study suggested a possible role of sustained adjuvant endocrine therapy for the ER-positive breast cancers with a long-term risk of relapse.

Taken together, tamoxifen monotherapy for five years seems to be suboptimal treatment in high-risk breast cancer patients and upfront use of AI would at least be beneficial for DFS. Since the risk of recurrence peaks early at 1-3 yr after primary therapy,*(14,15)* and that most patients with ER-positive cancers have a persistent risk of recurrence, it would be reasonable to offer most postmenopausal ER-positive cancer patients upfront use of AI. On the contrary, patients who have already started tamoxifen, should be advised to switch AI and patients who have already completed five years of tamoxifen therapy should consider the additional use of an AI.

Duration of aromatase inhibitors

The optimal duration of AI has not been determined. The 100-month analysis of the ATAC trial demonstrated a significantly larger carryover effect after five years of anastrozole compared with tamoxifen.*(4)* However, it is too early to say that five years of upfront AI use is enough. Rather, the optimal duration of AI should be revealed by the results of the ongoing rerandomizaton trial of the MA.17R trial.

Which aromatase inhibitors?

There have been no results showing a direct comparison between AI; however, the Femara versus Anastrozole Clinical Evaluation (FACE) trial will compare the efficacy of letrozole with anastrozole in node-positive patients*(16)* and the MA.27 trial will compare the safety and efficacy of the upfront use of anastrozole with exemestane.*(17,18)* Until then, indirect comparison will have to suffice as a point of reference.

ADJUVANT HORMONAL THERAPY FOR PREMENOPAUSAL BREAST CANCERS

Adjuvant hormonal therapy for the premenopausal breast cancers is a little more complicated than in postmenopausals, since premenopausal women have functioning ovaries. Five years of tamoxifen use is the gold standard for the ER-positive premenopausal breast cancers; however, the duration of tamoxifen therapy, the role of ovarian function suppression, the duration of endocrine therapy, and the use of AI is the issues yet to be resolved.

Gold standard

The most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Oxford Overview*(1)* confirmed that five years of tamoxifen was associated with a significant reduction in recurrence and mortality, extending out to at least 15 yr after diagnosis. Therefore, tamoxifen has remained the gold standard for premenopausal women since early 1980s. The panels of the 2009 St Gallen Concensus Conference accepted five years of either tamoxifen or tamoxifen plus ovarian function suppression as the standard endocrine therapy for premenopausal women.*(2)*

Although tamoxifen is the gold standard of adjuvant hormonal therapy for the premenopausal women with breast cancers, chemotherapy has a key role in these patients. A combination of chemotherapy and tamoxifen has been demonstrated to be superior to either on their own in premenopausal women with high-risk ER-positive breast cancers.

Duration of tamoxifen

Five years of tamoxifen has been confirmed as significantly more effective than two years, with further reduction in the annual recurrence and mortality.*(1)* Since the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial*(19)* demonstrated that more than five years of tamoxifen was associated with a significantly worse DFS, five years has remained as the optimal duration of tamoxifen administration. However, the NSABP B-14 trial*(19)* included patients with ER-positive, node-negative, and those disease-free after five years of tamoxifen and only 26% were younger than 50 yr of age. The benefit of more than five years of tamoxifen in premenopausal and postmenopausal women remains unclear*(1)* and there may be a benefit to longer tamoxifen therapy in those patients with node-positive disease.*(20)* Two large trials of tamoxifen duration are still ongoing: the Adjuvant Tamoxifen, Longer Against Shorter (ATLAS)*(21,22)* and Adjuvant Treatment Tamoxifen to Offer More (aTTom)

trials for the premenopausal and postmenopausal women, respectively.*(23,24)* Both trials have shown some benefit through preliminary analysis;*(22,24)* however, further follow-up is required. Meanwhile, the optimal duration of tamoxifen remains an open question until results can confirm otherwise.

Addition of ovarian function suppression vs. chemotherapy

Several trials comparing luteinizing-hormone-releasing hormone (LHRH) analogs with chemotherapy as well as the LHRH meta-analysis have shown no significant difference in recurrence or death after recurrence.*(25)* However, none of these trials included tamoxifen, and therefore both arms were clinically suboptimal.

In the Oxford Overview, the efficacy of ovarian ablation was almost entirely lost in the presence of chemotherapy*(1)* and the addition of an LHRH agonist to chemotherapy alone or to chemotherapy and tamoxifen did not significantly reduce the risk of recurrence;*(25)* however, there was a significant benefit in women younger than 40 yr of age. The Intergroup 0101 trial demonstrated that no additional advantage with the addition of LHRH agonist, but there was a significant improvement in DFS and a nonsignificant trend to improved OS with the addition of combined tamoxifen and LHRH agonist.*(26)* There was also a trend for benefit with the addition of LHRH agonist after chemotherapy in women younger than 40 yr of age. All these results support that conclusion that tamoxifen has an additional benefit to chemotherapy and suggests that the addition of LHRH analogs would be beneficial for younger patients who remains premenopausal after chemotherapy.

Duration of ovarian function suppression?

The 2005 Oxford Overview demonstrated that there is no significant difference in the efficacy between ovarian ablation (OA) and OS and a trend against LHRH analogs.*(1)*

The positive results of long-term estrogen suppression in the postmenopausals shown in the MA.17 trial and a trend against LHRH analogs shown in the 2005 Oxford Overview raise the question of optimal duration for ovarian ablation and whether LHRH analog treatment for 2-3 yr is as effective as permanent ablation.

Aromatase inhibitors for the pre- or peri-menopausal women

Aromatase inhibitors are contraindicated in women with functioning ovaries because the suppression of peripheral aromatase results in the reduced feedback of estrogen to the hypothalamus and an increase in ovarian stimulation,*(27-30)* which causes cystic changes in the ovary.

Most women older than age 40 treated with chemotherapy will develop permanent amenorrhea.*(31,32)* However, Smith et al.*(29)* reported that the incidence of ovarian function recovery was increased by the use of AI up to 27% compared with 0-11% spontaneously in women older than 40.*(31,33)* Recovery of ovarian function has been associated with the return of premenopausal estradiol levels which would diminish or abolish the anticipated anticancer efficacy, and can cause unwanted pregnancy.*(29)*

Based on the data, the use of AI should be performed with caution in patients with chemotherapy-induced amenorrhea, and it is important to regularly monitor ovarian function in patients who are using AI after premature cessation of menstruation of chemotherapy.

Use of an AI after ovarian ablation or suppression is theoretically possible; however, no data exists to indicate the long-term effects of complete estrogen suppression in young women. The ABCSG -12 study, which compared the outcomes of ovarian function suppression in addition to either anastrozole or tamoxifen, recently reported that no significant difference in DFS was seen between two arms with a median follow-up of 47.8 months.*(34)* Longer follow-up results, two large IBCSG trials, and the SOFT and TEXT trials*(35)* may provide clarity to this issue.

CYP2D6 POLYMORPHISM AND CYP2D6 INHIBITORS

Tamoxifen itself has low affinity to ER, meanwhile its active metabolite forms, 4-hydroxytamoxifen and 4-

hydroxy-N-desmethyltamoxifen (endoxifen) which are mainly mediated by CYP2D6, are more potent than tamoxifen in their antiestrogenic effects.*(36-39)* Genetic polymorphisms of CYP2D6 can cause different CYP2D6 activity and are known to be quite different among ethnic groups, especially the CYP2D6*10 allele which is more commonly observed in Asians,*(40,41)* as compared with the *4 allele which is frequently observed in Caucasians.*(42,43)*

Since a previous report suggesting that *4/*4 genotypes tend to have a higher risk of disease recurrence,*(44)* a few studies have reported that Asian patients carrying homogenous *10 alleles are associated with a higher hazard ratio or poorer survival results.*(45-47)* Okishiro et al. suggested that CYP2D6*10/*10 genotype, which was mainly related with the Intermediate Metabolizer group, was not associated with prognosis in patients treated with tamoxifen,*(48)* and recent meta-analysis results could not demonstrate statistically significant differences according to CYP2D6 genotyping in terms of DFS and OS.*(49)*

Treatment with drugs that inhibit CYP2D6 may reduce the clinical benefit of tamoxifen by interfering with its bioactivation, particularly when these drugs are used for an extended period. Antidepressants have been widely prescribed in patients with breast cancer for treatment of depression, tamoxifen- related hot flashes, and various other indications.*(50-53)* Selective serotonin reuptake inhibitor (SSRI) antidepressants inhibit CYP2D6 to varying degrees. Paroxetine is an exceptionally potent CYP2D6 inhibitor, and is the only SSRI that exhibits mechanism based ("suicide") inhibition, resulting in the irreversible loss of enzyme function until new CYP2D6 can be synthesized.*(54-56)*

Kelly et al.*(57)* reported that paroxetine use during tamoxifen treatment was associated with an increased risk of death from breast cancer. Based on such results, when co-prescription of tamoxifen with an antidepressant is necessary, preference should be given to antidepressants that show little or no inhibition of CYP2D6.*(57)*

However, Dejentje et al.*(58)* did not show an association between concomitant CYP2D6 inhibitor use and breast cancer recurrence among patients treated with adjuvant tamoxifen but rather, demonstrated that poor tamoxifen adherence was associated with an increased risk of breast cancer events.

Although it is not clear whether CYP2D6 polymorphism and CYP2D6 inhibitors are critically related to the tamoxifen efficacy, clinicians should be careful in choosing antidepressants. When co-prescription with tamoxifen is necessary clinicians should also check the compliance of tamoxifen ingestion during follow-up.

ANDROGEN RECEPTOR EXPRESSION AS A MARKER FOR ENDOCRINE RESPONSIVENESS

The role of the androgen receptor (AR) in breast cancer has not yet been established. However, most authors cite that 60-70% of tumors are AR positive, which is comparable to or higher than that reported for ER and progesterone receptor.*(59,60)* Limited studies have demonstrated the role of AR as a prognostic factor and the clinical implication of AR expression in ER-positive breast cancer.*(60)* Further studies through both univariate and multivariate analysis adjusting for age, tumor size, nodal stage, and HER-2 status may give more information about AR expression in luminal subtypes that may be associated with survival outcomes.

CONCLUSION

Endocrine therapy is the key element in the management of endocrine responsive breast cancers. Five years of either tamoxifen or tamoxifen plus ovarian function suppression have been proposed as acceptable standards for premenopausal women, while AI should form part of standard endocrine therapy for the postmenopausal women. However, there are many issues to be answered and ongoing clinical trials will provide the necessary answers in the near future. Until then, it would be practical for clinicians to carefully evaluate the risk factors of patients, monitor the compliance of patients who are under endocrine therapy, and take care in choosing antidepressants when co-prescription with tamoxifen is necessary.

In the future, tailored treatment will be applied based on the target molecular profiling of the tumors, pharmacogenomics, and improved understanding of receptor signaling biology. More attention should be given to exploring molecular markers that could differentiate the subsets for such tailoring.

REFERENCES

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.
2. Goldhirsch A, Ingle JN, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol 2009;20:1319-29.
3. Coates AS, Keshaviah A, Thurlimann B, Mouridsen H, Mauriac L, Forbes JF, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol 2007;25:486-92.
4. Forbes JF, Cuzick J, Buzdar A, Howell A, Tobias JS, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008;9:45-53.
5. Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 2007;369:559-70.
6. Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005; 366:455-62.
7. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 2005;97:1262-71.
8. Jonat W, Gnant M, Boccardo F, Kaufmann M, Rubagotti A, Zuna I, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol 2006;7:991-6.
9. Ingle JN, Dowsett M, Cuzick J, Davies C. Aromatase inhibitors versus tamoxifen as adjuvant therapy for postmenopausal women with estrogen receptor positive breast cancer: meta-analyses of randomized trials of monotherapy and switching strategies. Cancer Res 2009; 69(2 Suppl). abstract #12.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Breast Cancer. v.1. 2007. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. accessed January 4th 2007.
11. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, Thurlimann B, Paridaens R, Smith I, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J Med 2009; 361:766-76.
12. Jakesz R, Gnant M, Greil R, Tausch C, Samonigg H, Kwasny W, et al. The benefits of sequencing adjuvant tamoxifen and anastrozole in postmenopausal women with hormone-responsive early breast cancer: 5 year-analysis of the ABCSG Trial 8. Breast Cancer Res Treat 2005;94(Suppl 1):S10. abstract #13.
13. Mouridsen HT, Giobbie-Hurder A, Mauriac L, Paridaens R, Colleoni M, Thuerlimann B, et al. BIG 1-98: A randomized double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. Cancer Res 2009;69(2 Suppl). abstract #13.
14. Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 1996;14:2738-46.
15. Elder EE, Kennedy CW, Gluch L, Carmalt HL, Janu NC, Joseph MG, et al. Patterns of breast cancer relapse. Eur J Surg Oncol 2006;32: 922-7.
16. De Boer R Sr, Burris HA, Monnier A, Mouridsen H, O'Shaughnessy JA, McIntyre K, et al. The Head to Head trial: Letrozole vs anastrozole as adjuvant treatment of postmenopausal patients with node positive breast cancer. J Clin Oncol 2006;24(18 Suppl):S582. abstract #10672.
17. Moy B, Elliott CR, Chapman J-AW, Pater JL, Ding Z, Goss PE. NCIC CTG MA.27: menopausal symptoms of ethnic minority women. Breast Cancer Res Treat 2006;100(Suppl 1):S144. abstract #3059.
18. North Central Cancer Treatment Group, National Cancer Institute and National Cancer Institute of Canada. Breast density, hormone levels, and anticancer drug levels in women with invasive breast cancer who are receiving exemestane or anastrozole. http://www.clinicaltrials.gov. accessed June 27th, 2007.
19. Fisher B, Dignam J, Bryant J, Wolmark N. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. J Natl Cancer Inst 2001;93:684-90.
20. Tormey DC, Gray R, Falkson HC. Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. Eastern Cooperative Oncology Group. J Natl Cancer Inst 1996;88:1828-33.
21. University of Oxford Clinical Trial Service Unit and Epidemiological Studies Unit. ATLAS: Adjuvant Tamoxifen Longer Against Shorter. Oxford: University of Oxford. http://www.ctsu.ox.ac.uk/projects/atlas. accessed July 25th 2007.
22. Peto R, Davies C. ATLAS (Adjuvant Tamoxifen, Longer Against Shotrer): international randomized trial of 10 versus 5 years of adjuvanr tamoxifen among 11500 women-preliminary results. The 30th Annual San Antonio Breast Cancer Symposium. 2007. abstract #48.
23. National Cancer Research Network. Adjuvant treatment tamoxifen offers more. http://www.ncrn.org.uk/portfolio/data. accessed June 27th, 2007.
24. Gray RG, Rea DW, Handley K, Marshall A, Pritchard MG, Perry P, et al. aTTom (adjuvant Tamoxifen-To offer more): Randomized

trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER+) or ER untested breast cancer-Preliminary results. J Clin Oncol 2008;26(15 Suppl):S10. abstract #513.
25. Cuzick J, Ambroisine L, Davidson N, Jakesz R, Kaufmann M, Regan M, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 2007;369:1711-23.
26. Davidson NE, O'Neill AM, Vukov AM, Osborne CK, Martino S, White DR, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol 2005; 23:5973-82.
27. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med 2003;348:2431-42.
28. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001;75:305-9.
29. Smith IE, Dowsett M, Yap YS, Walsh G, Lonning PE, Santen RJ, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol 2006;24:2444-7.
30. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 2005;23:619-29.
31. Bines J, Oleske DM, Cobleigh MA. Ovarian function in premenopausal women treated with adjuvant chemotherapy for breast cancer. J Clin Oncol 1996;14:1718-29.
32. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year after breast cancer diagnosis. J Clin Oncol 1999;17:2365-70.
33. Bianco AR, Del Mastro L, Gallo C, Perrone F, Matano E, Pagliarulo C, et al. Prognostic role of amenorrhea induced by adjuvant chemotherapy in premenopausal patients with early breast cancer. Br J Cancer 1991;63:799-803.
34. Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Postlberger S, Menzel C, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360:679-91.
35. Francis P, Fleming G, Nasi ML, Pagani O, Perez E, Walley B. Tailored treatment investigations for premenopausal women with endocrine responsive (ER+ and/or PgR+) breast cancer: The SOFT, TEXT, and PERCHE trials. Breast 2003;12(Suppl 1):S44. abstract #104.
36. Johnson MD, Zuo H, Lee KH, Trebley JP, Rae JM, Weatherman RV, et al. Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. Breast Cancer Res Treat 2004;85:151-9.
37. Lim YC, Li L, Desta Z, Zhao Q, Rae JM, Flockhart DA, et al. Endoxifen, a secondary metabolite of tamoxifen, and 4-OH-tamoxifen induce similar changes in global gene expression patterns in MCF-7 breast cancer cells. J Pharmacol Exp Ther 2006;318:503-12.
38. Borgna JL, Rochefort H. Hydroxylated metabolites of tamoxifen are formed in vivo and bound to estrogen receptor in target tissues. J Biol Chem 1981;256:859-68.
39. Lim YC, Desta Z, Flockhart DA, Skaar TC. Endoxifen (4-hydroxy-N-desmethyl-tamoxifen) has anti-estrogenic effects in breast cancer cells with potency similar to 4-hydroxy-tamoxifen. Cancer Chemother Pharmacol 2005;55:471-8.
40. Lee SJ, Lee SS, Jung HJ, Kim HS, Park SJ, Yeo CW, et al. Discovery of novel functional variants and extensive evaluation of CYP2D6 genetic polymorphisms in Koreans. Drug Metab Dispos 2009;37: 1464-70.
41. Li H, Feng L, Xu Y, Yao L, Ouyang T, Li J, et al. The association of CYP2D6 *10 polymorphism with breast cancer risk and clinicopathologic characteristics in Chinese women. Acta Oncol 2006;45: 597-601.
42. Sachse C, Brockmoller J, Bauer S, Roots I. Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences. Am J Hum Genet 1997;60:284-95.
43. Kubota T, Yamaura Y, Ohkawa N, Hara H, Chiba K. Frequencies of CYP2D6 mutant alleles in a normal Japanese population and metabolic activity of dextromethorphan O-demethylation in different CYP2D6 genotypes. Br J Clin Pharmacol 2000;50:31-4.
44. Goetz MP, Rae JM, Suman VJ, Safgren SL, Ames MM, Visscher DW, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol 2005; 23:9312-8.
45. Lim HS, Ju Lee H, Seok Lee K, Sook Lee E, Jang IJ, Ro J. Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. J Clin Oncol 2007;25:3837-45.
46. Xu Y, Sun Y, Yao L, Shi L, Wu Y, Ouyang T, et al. Association between CYP2D6 *10 genotype and survival of breast cancer patients receiving tamoxifen treatment. Ann Oncol 2008;19:1423-9.
47. Kiyotani K, Mushiroda T, Imamura CK, Hosono N, Tsunoda T, Kubo M, et al. Significant effect of polymorphisms in CYP2D6 and ABCC2 on clinical outcomes of adjuvant tamoxifen therapy for breast cancer patients. J Clin Oncol 2010;28:1287-93.
48. Okishiro M, Taguchi T, Jin Kim S, Shimazu K, Tamaki Y, Noguchi S. Genetic polymorphisms of CYP2D6 10 and CYP2C19 2, 3 are not associated with prognosis, endometrial thickness, or bone mineral density in Japanese breast cancer patients treated with adjuvant tamoxifen. Cancer 2009;115:952-61.
49. Seruga B, Amir E. Cytochrome P450 2D6 and outcomes of adjuvant tamoxifen therapy: results of a meta-analysis. Breast Cancer Res Treat 2010;122:609-17.
50. Chubak J, Buist DS, Boudreau DM, Rossing MA, Lumley T, Weiss NS. Breast cancer recurrence risk in relation to antidepressant use after diagnosis. Breast Cancer Res Treat 2008;112:123-32.
51. Coyne JC, Palmer SC, Shapiro PJ, Thompson R, DeMichele A. Distress, psychiatric morbidity, and prescriptions for psychotropic medication in a breast cancer waiting room sample. Gen Hosp Psychiatry 2004;26:121-8.
52. Loprinzi CL, Barton DL, Sloan JA, Novotny PJ, Dakhil SR, Verdirame JD, et al. Mayo Clinic and North Central Cancer Treatment Group

hot flash studies: a 20-year experience. Menopause 2008;15:655-60.
53. Reich M, Lesur A, Perdrizet-Chevallier C. Depression, quality of life and breast cancer: a review of the literature. Breast Cancer Res Treat 2008;110:9-17.
54. Bertelsen KM, Venkatakrishnan K, Von Moltke LL, Obach RS, Greenblatt DJ. Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: comparison with fluoxetine and quinidine. Drug Metab Dispos 2003;31:289-93.
55. Venkatakrishnan K, Obach RS. In vitro-in vivo extrapolation of CYP2D6 inactivation by paroxetine: prediction of nonstationary pharmacokinetics and drug interaction magnitude. Drug Metab Dispos 2005;33:845-52.
56. Venkatakrishnan K, Obach RS, Rostami-Hodjegan A. Mechanism-based inactivation of human cytochrome P450 enzymes: strategies for diagnosis and drug-drug interaction risk assessment. Xenobiotica 2007;37:1225-56.
57. Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. BMJ 2010;340:c693.
58. Dezentje VO, van Blijderveen NJ, Gelderblom H, Putter H, van Herk-Sukel MP, Casparie MK, et al. Effect of concomitant CYP2D6 inhibitor use and tamoxifen adherence on breast cancer recurrence in early-stage breast cancer. J Clin Oncol 2010;28:2423-9.
59. Park S, Koo J, Park HS, Kim JH, Choi SY, Lee JH, et al. Expression of androgen receptors in primary breast cancer. Ann Oncol 2010;21: 488-92.
60. Castellano I, Allia E, Accortanzo V, Vandone AM, Chiusa L, Arisio R, et al. Androgen receptor expression is a significant prognostic factor in estrogen receptor positive breast cancers. Breast Cancer Res Treat. Epub 2010 Feb 3. DOI: 10.1007/s10549-010-0761-y.