Review

Current issues in adjuvant hormonal therapy for early breast cancer

John Carpenter.
Emeritus Professor of Medicine (Hematology/Oncology), University of Alabama at Birmingham.

***Corresponding author**: Emeritus Professor of Medicine (Hematology/Oncology), University of Alabama at Birmingham. BDB 684, 1720 Second Avenue South, Birmingham, AL 35294-3300, USA. Email: jtc4321@bellsouth.net or jtc@uab.edu. Tel: 1-205-910-8886 or 1-205-934-2084
Citation: John Carpenter. Current issues in adjuvant hormonal therapy for early breast cancer. Cancer Research Frontiers. 2016 Feb; 2(1): 105-111. doi: 10.17980/2016.105

Competing Interests: The author declares no competing financial interests.
Received Nov 2, 2015; Revised Feb 12, 2016; Accepted Feb 15, 2016. Published Feb 29, 2016

ABSTRACT
Breast cancer remains the most common malignancy of women in the world. The majority of tumors contain nuclear receptors for estrogen (ER) and/or progesterone (PR). For these tumors, estrogen deprivation, using ovarian function suppression (OFS), drugs which block the synthesis of estrogen, or drugs which interfere with the effects of estrogen on tumor cells, constitutes the main treatment modality which prolongs survival. Current guidelines recommend tamoxifen or an aromatase inhibitor (AI) for 5-10 years after local therapy and after chemotherapy if it is used. No prospective trials reported to date have evaluated any adjuvant hormonal therapy for longer than 10 years duration or more than 5 years of an adjuvant AI. This review includes discussion of newer issues in hormonal therapy, including the extended use of hormonal therapy, the interruption of ovarian function in high-risk young women, the relative efficacy of AIs compared to tamoxifen, the adjuvant use of bisphosphonates, and the identification of groups of patients who may gain more or less benefit from adjuvant estrogen deprivation. As understanding of the biology of breast cancer increases, one can expect to see a corresponding increase in the precision of treatment recommendations for individual patients.
KEYWORDS: breast cancer, hormonal therapy, adjuvant

BACKGROUND

Breast cancer remains the most common malignancy of women in the world, including the U.S. The majority of these tumors contain nuclear receptors for estrogen and/or progesterone, indicating that estrogen plays an important role in cell growth and differentiation. Beatson (1) in 1896 showed that removal of the ovaries led to temporary tumor shrinkage in some young women with advanced breast cancer. Removal of ovaries and other procedures and drugs interfering with estrogen action have been used for palliation in women with advanced breast cancer since then. The idea of using adjuvant systemic therapy was advanced by Dr. Bernard Fisher and his group beginning in the 1960s (2,3). The estrogen receptor was described as the mechanism for estrogen action by Jensen (4) in 1962.

Tamoxifen, originally developed as a contraceptive, was found to have antiestrogenic action in 1971 (5). It was studied extensively in the laboratory by Jordan and his colleagues (6), then used extensively in the clinic, first in women with advanced breast cancer, then in the adjuvant setting. Tamoxifen binds the estrogen receptor but modulates a different set of genes than estradiol does, so that it interferes with cell growth. Side effects of tamoxifen include thromboembolism, endometrial hyperplasia and endometrial cancer, as well as vasomotor symptoms. Baum presented the

Table: Recent Studies Affecting Adjuvant Hormonal Therapy

Adjuvant	Main Finding	Author(reference)
Adjuvant hormonal therapy	No benefit from adjuvant hormonal therapy in ER 1-10% +	Yi (7)
	Oncotype Recurrence score 1-10 in low risk tumors 99% DFS at 5 years without chemotherapy. No benefit from chemotherapy for luminal A cancers	Sparano (14) Nielsen (24)
	Meta-analysis shows AIs 30% more effective than tamoxifen	EBCTCG (15)
Bisphosphonates	Adjuvant bisphosphonates reduce mortality by 18%.	EBCTCG (16)
Ovarian function suppression (OFS)	Adjuvant OFS may improve survival in some but risks remain to be defined.	Pagani (27) and Francis (28)

original tamoxifen adjuvant results in 1982 (7), using the drug for 2 years after local treatment. Based on prospective studies, the recommended duration of treatment has now been extended out to 10 years (8,9). In the 1980's aromatase inhibitors (AIs) were introduced into the clinic; these drugs bind to the enzyme aromatase and thus inhibit the synthesis of estradiol by about 95%. AI side-effects are somewhat different and include arthralgias (which can be severe), bone loss, vaginal and perineal dryness, and vasomotor symptoms. Both groups of drugs are effective, but a recent overview reveals that AIs are about 30% more effective than tamoxifen while being taken (10) and have a similar carry-over effect.

Tamoxifen is effective in women of any age, but may be poorly tolerated in postmenopausal women and may cause endometrial cancer in women who are no longer cycling, so it is used less in postmenopausal women. AIs are given in a dose which is insufficient to inhibit ovarian aromatase, so they are effective only in women with no remaining ovarian function. In addition, the resulting decrease in estrogen levels leads to increased pituitary and hypothalamic activity with resulting increased gonadatropin levels in premenopausal women (11). Determination of menopausal status can be tricky in women who experience cessation of menses due to chemotherapy. About 90% of women who will restart menses do so within 2 years of the last cycle (12,13). Blood tests such as FSH may be misleading during this period of time because they reflect the current status of ovarian function, but not necessarily the eventual status. In this group of women, use of tamoxifen for 2-3 years after the last menstrual cycle is suggested, followed by changing to an AI only if FSH is elevated after 4 weeks off of tamoxifen. Questions addressed by recently reported clinical trials have included longer durations of AI use and the role of interruption of ovarian function in addition to current hormonal therapy for premenopausal women.

Current guidelines issued by the American Society of Clinical Oncology (ASCO)[14] and by the National Comprehensive Cancer Center Network version 3, 2015, accessed 10/28/15 (NCCN) for adjuvant

hormonal therapy call for 10 years of adjuvant tamoxifen in women who remain premenopausal, and for a change to an AI for 5 years after 3-5 years of tamoxifen for those who become postmenopausal during the early years of treatment. No clinical trial to date has reported results from more than 10 years of adjuvant hormonal therapy; the guidelines thus recommend stopping endocrine therapy at 10 years. That recommendation is not evidence based; it simply reflects the lack of evidence available for any hormonal treatment after 10 years. For perimenopausal women, the best approach is probably to proceed as described in the previous paragraph above, that is, to begin with tamoxifen, with later change to an AI after several years, only when FSH level becomes elevated after 4 weeks off of tamoxifen. For postmenopausal women, more choices are included in the guidelines. These include 10 years of tamoxifen, 5 years of an AI, an AI for 2-3 years followed by tamoxifen through 5 years, or some period of tamoxifen (usually 3-5 years) followed by 5 years of an AI. For those who don't tolerate AIs, tamoxifen may be substituted. No use of more than 5 years of an AI is included because none has been reported in clinical trials to date; similarly, guidelines recommend stopping hormonal treatment after 10 years. Interestingly, the original preclinical results by Jordan et al found that prolonged estrogen deprivation was most effective (15); it seems likely that clinical results in human breast cancer may recapitulate this finding.

Guidelines do not help in deciding about extended use of adjuvant hormonal therapy after 5 years of treatment with aromatase inhibitors, because there are simply no data from clinical trials on this point. It is likely that, at least for high risk women, many may benefit from more extended use, but the balance between benefit and side effects remains unknown at present. It is likely that both disease control and long term toxicities will be affected by their use. In nearly every trial reported to date which compared different durations of adjuvant hormonal therapy for patients with breast cancer, longer duration of therapy has been more effective and the benefit of longer treatment has far outweighed the risks. This provides no assurance that studies in progress will report similar findings.

A word about guidelines: guidelines are based on published evidence from prospective clinical trials. They do not ordinarily extrapolate, and clinical questions not answered by clinical trial results are generally not included. The trials include some 3% of women with breast cancer in the U.S (16). These women are healthier with fewer comorbidities than those not studied (most likely related to age) (17) and their median age is 49 years (18), in contrast to the median age of women at the time of diagnosis with breast cancer, which is now 61 (19). Thus they represent best available evidence- based recommendations for treatment. Recommendations for individual patients should also include allowances for age, comorbidities, differences in drug tolerance, and individual patient preferences. Guidelines should not be misconstrued as being one-size-fits-all.

NEWER ISSUES

1. Groups with no benefit and with 99% benefit

Two subsets of patients have been described whose characteristics may affect the use of hormonal adjuvant treatment. The first of these is that of patients whose tumor is positive for estrogen receptors in 1-9% of cells. A report by Yi et al (20) in 2014 showed that 2.6% of their group of 9,639 patients had staining for estrogen receptors (ER) in 1-9% of cells. This level of staining is reported as positive using current guidelines (21). Yet this patient group was younger and had a more advanced stage of disease. Their survival resembled that of patients with triple negative disease; it was the same with or without adjuvant hormonal treatment. A previous small study from 2012 (22) showed that patients with ER staining in 1-9% of cells had lower levels of ESR-1 mRNA, lower ER gene signature scores, and included only 8% luminal tumors, compared to 50% in those with higher levels of ER staining. Their survival was intermediate between the group with 10% or more cells staining for ER and those with triple negative disease. It is reasonable to prescribe endocrine therapy for patients in this group, but wise not to depend on it as the main treatment modality. Further analysis of their tumors should certainly be considered and use of adjuvant chemotherapy should also be considered strongly, based on this information.

The other special subgroup was recently described by Sparano et al (23), giving us the first reported results from the TAILOR-X trial done in the U.S. In that prospective study of 10,253 eligible patients with hormone receptor positive, HER-2 negative and axillary node negative disease enrolled, 1,626 (16% of the

group) who had Oncotype DX recurrence scores of 0-10 were assigned to receive endocrine therapy alone without chemotherapy. The rate of distant disease-free survival at 5 years was 99.3%, and overall survival was 98%. This trial shows conclusively that patients in that group can be treated with adjuvant endocrine therapy alone after local treatment, with an expectation of excellent outcome. . A similar finding was reported recently at the 2015 San Antonio Breast Cancer Symposium by Nielsen et al (24). Intrinsic subtyping was done on tissue microarrays from 709 breast cancers from the Danish Breast Cancer Group 77B Randomized Trial. In that trial from the late 1970's, patients were randomized to receive adjuvant chemotherapy or to a control arm. Patients with luminal A cancers had no reduction in invasive recurrence; hazard ratio was 1.07 (95% confidence intervals of 0.53-2.14, p = 0.86). Survival at 25 years was similarly unaffected. Since 99% of patients in the Sparano trial had tumors that were positive for estrogen receptors and 98% had tumors positive for progesterone receptors, nearly all of the patients in the Sparano trial would be included in this group of patients.

2. Adjuvant AIs are more effective than tamoxifen

In October of 2015, the Early Cancer Trialists' Collaborative Group (EBCTCG) reported the results of their meta-analysis of all published randomized trials comparing tamoxifen to AIs (10). The strength of this group's previous analyses is that they have been able to detect small but clinically important differences in treatments which were not apparent in previous smaller individual trials. They found that during treatment, relapse rates were 30% lower and mortality was 14% lower when patients were receiving AIs. In the period after treatment, there was no difference in recurrence rates. Non-breast cancer mortality rates were similar. They concluded that 5 years of adjuvant AI treatment reduces breast cancer mortality by about 40%, compared to the roughly 25% seen with tamoxifen. Of the deaths observed by 10 years of followup, more than half in both groups were not due to breast cancer. This finding will certainly provoke a reconsideration of the guidelines for adjuvant hormonal therapy for postmenopausal women. At least 5 years of treatment with an AI is likely to become the gold standard, with tamoxifen reserved for those who do not tolerate AIs. The NSABP B 42 and MA-17R trials comparing 5 vs. 10 years of adjuvant AI treatment are awaited with particular interest, given these new findings. The risk of recurrence persists for at least 15 years after initial treatment, probably longer; it is highest in the first 5 years after diagnosis, but persists at a lower annual rate after that time, which is related to the characteristics of the original tumor. There is no risk of recurrence so low as to be acceptable to many patients. This ensures that longer use of hormonal treatment will continue to be of interest.

3. Adjuvant bisphosphonates increase survival

Given the bone loss which occurs in many women who take AIs, the report of adjuvant bisphosphonate treatment reported in the same October 3, 2015 issue of the Lancet (25) will also be pertinent. The EBCTCG also reported that adjuvant bisphosphonate treatment 1) appears to be effective only in postmenopausal women and that 2) in that group, adjuvant bisphosphonates reduced recurrence by 30%, distant recurrence by 27%, and breast cancer mortality by 15%. Since these agents also provide effective treatment for bone loss and are known to prevent fractures, addition of adjuvant bisphosphonates may be especially helpful in postmenopausal women. Remaining issues include the fact that bisphosphonates are not approved for this indication in the U.S. and may likely not be covered by insurance. An early report presented at the 2015 San Antonio Breast Cancer Symposium (26) suggests a similar effect from adjuvant denosumab.

4. Adjuvant ovarian function suppression

The last and most contentious new information is the reports of the SOFT and TEXT trials on the role of ovarian function suppression (OFS) in women with early breast cancer who remain premenopausal (premenopausal estradiol level) after chemotherapy for early breast cancer or after local treatment in those for whom tamoxifen alone would be suitable (27,28). Subjects in the SOFT trial were randomized to tamoxifen alone, tamoxifen and OFS, or to exemestane and OFS. Those in the TEXT trial were randomized to OFS and either tamoxifen or exemestane. Results were reported at about 5 years of followup. Overall there was no significant difference in disease free survival (DFS) among the 3 groups. The TEXT trial, reported earlier, showed an absolute 4% difference in disease-

free survival of exemestane/OFS over tamoxifen/OFS. The later SOFT trial results showed a 2% absolute difference in disease-free survival favoring tamoxifen/OFS over tamoxifen alone which was not significant (p=0.10). Preplanned multivariable analysis, however, showed a 4% improvement in freedom from recurrence in those higher risk subjects who had received chemotherapy, although not in those who did not. This difference was most striking in women younger than age 35, where recurrences occurred in 1/3 vs. 1/6 of patents by 5 years. This result will lead to increased recommendation for OFS in addition to tamoxifen or exemestane for very young women and for those at high risk, such as those with multiple involved axillary nodes.

This results of SOFT and TEXT trials are more complex than it seems at first glance. The improvements seen are in recurrence, not in survival, and are in the same 2-4% range seen with other improvements in breast cancer treatment. Overall survival may be a more suitable primary endpoint, since other subsequent treatment(s) may also affect survival. A benefit of comparable magnitude might be expected with an additional 5 years of tamoxifen, or with an additional 5 years of an AI after completing tamoxifen for those who have reached menopause by that time. Treatment after 5 years was not defined in the SOFT and TEXT trials. Five year survival was slightly but not significantly lower in the tamoxifen/OFS group, HR=1.14; 8 year results from the Austrian trial showed more deaths in those who received anastrazole/OFS compared to those who received tamoxifen/OFS (p=0.030)[29]. Longer followup will clearly be needed. Toxicities in the SOFT and TEXT trial were substantial, with about 1/3 experiencing grade 3 and 4 toxicities related to OFS. Early removal of ovaries carries with it an increased risk of death over time (30, 31), particularly from cardiovascular disease and from cancers of lung and bowel (30). Whether the early reduction in deaths seen in the SOFT trial will hold up over time, and whether it will be of sufficient size to counterbalance the associated risk of death from other causes remain to be seen. The high rate of serious endocrine related toxicities and depression will make OFS an unacceptable choice for some women. Experienced clinicians are well aware that tolerance of estrogen deprivation or removal of ovaries varies to a remarkable extent in individual women. Compliance with treatment was less than ideal in the SOFT and TEXT studies; methods to improve tolerance of endocrine side effects are sorely needed. It will be interesting to see just how many of the above factors are incorporated into upcoming guidelines.

FURTHER COMMENTS

Endocrine treatment of early breast cancer continues to evolve, based on a better scientific understanding of its short- and long-term effects, and on the results of multiple ongoing clinical trials. The new information covered above will help to define more precisely what may be appropriate treatment for individual patients. It will also certainly provide questions to be addressed in further clinical trials.

ABBREVIATIONS

AI, aromatase inhibitor
ASCO, American Society of Clinical Oncology
DFS, disease-free survival
EBCTSG, Early Breast Cancer Trialists' Collaborative Group
ER, estrogen receptor
ESR-1, the gene which encodes the estrogen receptor protein
FSH, follicle stimulating hormone
mRNA, micro ribose nucleic acid
NSABP, National Surgical Adjuvant Breast and Bowel Project
NCCN, National Comprehensive Cancer Center Network
OFS, ovarian function suppression
PR, progesterone receptor
SOFT, Suppression of Ovarian Function Trial
TEXT, Tamoxifen and Exemestane Trial

REFERENCES

1. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. The Lancet 1896 July18; 148(3803): 162-65.
2. Fisher B, Carbone P, Economou SG, Frelick R, Glass A, Lerner H, et al. l-phenylalanine mustard (L-PAM) in the management of primary breast cancer. A report of early findings. N Engl J Med 1975 Jan 16; 292(30): 117-22.
3. Fisher B, Fisher ER, Redmond C. Ten-year results from the National Surgical Adjuvant Breast and

Bowel Project (NSABP) clinical trial evaluating the use of L-phenylalanine mustard (L-PAM) in the management of primary breast cancer. J Clin Oncol 1986 Jun; 4(6): 929-41

4. Jensen EV, Jacobson HI. Basic guides to the mechanism of estrogen action. Recent Progr Hormone Res 1962;18:387-414.
5. Cole MP, Jones CTA, Todd IDH. A New Anti-oestrogenic Agent in Late Breast Cancer. An Early Clinical Appraisal of ICI46474. Br J Cancer 1971 June;25:270-75. DOI:10.1038/bjc.1971.33
6. Jordan VC, Brodie AMH. Development and Evolution of Therapies Targeted to the Estrogen Receptor for the Treatment and Prevention of Breast Cancer. Steroids. 2007 January; 72(1):7-25. DOI: 10.1016/j.steroids.2006.10.009
7. Baum M, Brinkley M, Dossett JA,McPherson K, Patterson JS, Rubens RD, et al. Controlled trial of tamoxifen as adjuvant agent in management of Early Breast Cancer: Interim analysis at four years by the Novaldex Adjuvant Trial Organisation. Lancet 1983 5 Feb; 321(8319):257-61.
8. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer, ATLAS, a randomised trial. Lancet. 2013 Mar 9;381(9869):805-16. DOI:10.1016/S0140-6736(12)61963-1
9. Gray RG, Rea K, Handley K, Bowden SJ, Perry P, Earl HM, et al. ATTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol 2013 June 20 Supplement; 31(18):abstract 5.
10. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Dowsett M, Forbes JF, Bradley R, Ingle J, Aihara T, et al. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015 Oct 3;386(10001):1341-52. DOI: 10.1016/S0140-6736(15)61074-1
11. Miller, WR. Biological rationale for endocrine therapy in breast cancer. Best Pract Res Clin Endocrinol Metab 2004 Mar;18(1):1-32. DOI:10.1016/S1521-690X(03)00044-7
12. Sukumvanich P, Case LD, Van Zee K, Singletary E, Paskett ED, Petrek JA, et al . Incidence and Time Course of Bleeding After Long-Term Amenorrhea After Breast Cancer Treatment. Cancer. 2010 July 1;116:3102-11. DOI: 10.1002/cncr.25106.
13. Torino F, Barnabei A, De Vecchis L, Appetecchia M, Strigari L, Corsello SMl. Recognizing menopause in women with amenorrhea induced by cytotoxic chemotherapy for endocrine-responsive early breast cancer. Endocrine-Related Cancer 2012 April 1;19:R21-R33. DOI: 101530/ERC-11-0199
14. Burstein HJ, Temin S, Anderson H, Buchholz TA, Davidson NE, Gelmon KE, et al. Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. J Clin Oncol. 2014 July 20;32:2255-69. DOI:10.1200/JCO.2013.54.2258

15 Jordan VC, Dix CJ, Allen KE. The effectiveness of long term tamoxifen treatment in a laboratory model for adjuvant hormone therapy of breast cancer. Adj Ther Cancer 1979;2:19-26.

16.Murphy VH, Krumholz HM, Gross GP. Participation in Cancer Clinical Trials: Race-, Sex-, and Age-Based Disparities. JAMA 2004 June 9; 291(22)2720-26.

17.Guralnik JM. Assessing the Impact of Comorbidity in the Older Population. Ann Epidemiol 1996 Sep;6(5):376-80.

18. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Albain KS. Underrepresentation of Patients 65 Years of Age or Older in Cancer-Treatment Trials. New Engl J Med 1999 Dec 30;341(27):2061-67.

19. Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2012.http://seer/cancer.gov/csr/1075_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.Bethesda, MD: National Cancer Institute, 2015.

20.Yi M, Huo L, Koenig KB, Mittendorf EA, Meric-Bernstam F, Kuerer HM, et al. Which threshold for ER positivity? a retrospective study based on 9639 patients. Ann Oncol. 2014 May;25(5):1004-11. DOI: 10.1093/annonc/mdu053

21. Hammond ME, Hayes DF, Dowsett M, Allred DC, Haggert KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin

Oncol. 2010 June 1;28(16):2784-95. DOI: 10.1200/JCO.2009.25.6529

22. Iwamoto T, Booser D, Valero V, Murray JL, Koenig K, Esteva FJ, et al. Estrogen receptor (ER)mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry. J Clin Oncol 2012 March 1(7);30:729-34. DOI: 10.1200/JCO.2011.36.2574
23. Sparano JA, Gray RJ, Makower DF, Pritchard KI, Albain KS, Hayes DF, et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2015 Nov 19;373(21):2005-14. DOI 10:1056NEJMoa1510764
24. Nielsen TO, Jensen M-B, Gao D, Leung S, Burugu S, Liu S, et al. High risk premenopausal luminal A breast cancer patients derive no benefit from adjuvant chemotherapy: Results from DBCG77B randomized trial. San Antonio Breast Cancer Symposium Dec 2015 Abstract #S1-08
25. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Coleman R, Powles T, Paterson A, Gnant M, Anderson S, et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet. 2015 Oct 3;386(10001):1353-61. doi: 10.1016/S0140-6736(15)60908-4.
26. Gnant M, Pfeiler G, Dubsky PC, Hubalek M, Grell R, Jaakesz R, et al. The impact of adjuvant denosumab on disease-free survival: Results from 3,425 postmenopausal patients of the ABCSG-18 trial. 2015 San Antonio Breast Cancer Symposium Abstract S2-02.
27. Pagani O, Regan MM, Walley WA, Fleming GF, Colloeoni M, Lang I, et al. Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2014 July 10;371:107-18. DOI: 10.1056/NEJMoa1404037
28. Francis PA, Regan MM, Fleming GF,Lang I,Ciiruelos E, Bellet M, et al. Adjuvant Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2015 Jan 29;372:436-46. DOI: 10.1056/NEJMoa1412379
29. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Knauer M, Moi M, et al. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrazol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. Ann Oncol 2015 Feb;26:313-320. DOI: 10.1093/annonc/mdu544
30. Parker WH, Feskanich D, Broder MS, Chang E, Shoupe D, Farquhar C, et al. Long-Term Mortality Associated With Oophorectomy Compared With Ovarian Conservation in the Nurses' Health Study. Obstetrics & Gynecology 2013 April;121(4):709-16. DOI: 10.1097/AOG.Ob013e3182864350
31. Parker WH. Ovarian conservation versus bilateral oophorectomy at the time of hysterectomy for benign disease. Menopause 2014 Feb2(2);21(2):192-94. DOI: 10.1097;gme.Ob013e31829bc0a0