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Original Article

Practical consensus recommendations on ovarian suppression in early breast cancer (adjuvant)

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Abstract

Substantial survival benefits exist for patients with early-stage breast cancer who undergo treatment with single-modality ovarian suppression, but its value is uncertain. Expert oncologist discussed to determine whether additional benefits exist with ovarian suppression plus multiple adjuvant therapy which provides a new treatment option that reduces the risk of recurrence in early breast cancer. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at this practical consensus recommendations for the benefit of community oncologists.

Key words: AI, exemestane, LHRH agonist, menopausal status, monitoring, tamoxifen

Introduction

Approximately one third of newly diagnosed invasive breast cancers occur in women under 50 years of age.[1,2] It is likely that more women will be diagnosed with early-stage breast cancer at younger ages as a result of demographic and lifestyle changes, as well as progress in screening.[3,4] Ovarian suppression is the oldest systemic treatment available to patients with breast cancer.[5] It was also the first systemic adjuvant treatment to be tested in a randomized trial in oncology.[6] Since then, several trials have evaluated its potential role as an adjuvant therapy in patients with early breast cancer.[7] Although there is evidence that ovarian suppression affords an overall survival benefit at least up to 20 years of follow-up in premenopausal patients,[7] its use is still highly controversial.

Hormone receptor (HR)–positive breast cancer is the most common subtype,[8] and decades of clinical trials optimizing adjuvant endocrine therapies have led to significantly improved outcomes.[9] Most recently, large international trials have shown decreased breast cancer recurrence rates with extended endocrine therapy[10] and adjuvant ovarian suppression.[11,12]

Expert group of oncologist meet in the update in oncology-X-2017 to discuss on available strategies for treatment of ovarian suppression in early breast cancer by adjuvant therapies.

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital and the group met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer out of these we would discus about ovarian suppression in EBC (Adjuvant) in this chapter. While the discussions will take the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.[13,14]

The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the 250 oncologist including medical oncologists, radiation oncologists, surgical oncologists, molecular oncologists and radiologists who were present in the update in oncology-X-2017 was taken into consideration by the expert panel. The expert group was chaired by Dr. Sudeep Gupta whereas the discussions were moderated by Dr. Manish Singhal and Dr. T P Sahoo. The core expert group consists of Dr. Anil Singhvi, Dr.Vivek Kaushal, Dr.Sajjan Rajpurohit, Dr. K M Parthasarthi, and Dr. Amish Vora. Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.[15-17] The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their personal experiences, make comments and record dissent while voting for the consensus statements. Total of Six broad question categories were part of the expert group discussions [Tables 1-7].

Adjuvant endocrine therapy with tamoxifen has been recommended for premenopausal women with hormone receptor–positive breast cancer (positive for estrogen receptor, progesterone receptor, or both) during the past 15 years.[18,19] The value of therapeutic suppression of ovarian estrogen production in premenopausal women who receive tamoxifen is uncertain.[20] The American Society of Clinical Oncology endorsed guidelines recommending that ovarian ablation or suppression (hereafter, ovarian suppression) not be added routinely to adjuvant therapy in premenopausal women.[21] Chemotherapy-induced ovarian suppression (amenorrhea) is correlated with a reduced risk of relapse[22-24] but is less

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Table 1: Question categories addressed by the update in oncology-X-2017

Broad question title
Case 1-38-year-old premenopausal lady diagnosed with infiltrating duct carcinoma left breast. She undergoes modified radical mastectomy. HPE results - T2N1M0. ER positive, PR positive, HER 2/neu negative. After adjuvant chemotherapy, she needs hormonal therapy
Question 1 - Will you opt for ovarian suppression?
Question 2 - With ovarian suppression will you opt for SERM or AI?
Question 3 - In HR negative patient, will you opt for LHRH agonist for fertility preservation
Three additional questions on the controversial topics added by the moderators on which the expert panel gave their consensus
Question 4 - How do we monitor the postmenopausal status?
Question 5 - Will the number of nodes involved influence your decision?
Question 6 - For node negative cases, your choice will be?
Update in oncology-X-2017

ER=Estrogen receptor, PR=Progesterone receptor, HER 2=Human epidermal growth factor receptor 2, SERM=Selective estrogen receptor modulator, AI=Aromatase inhibitor, HR=Hormone receptor, LHRH=Luteinizing hormone-releasing hormone

Table 2: Question 1 - Will you opt for ovarian suppression?

Options (%)	Yes	No
Percentage of polled oncologists	67	33

Expert group consensus: Ovarian suppression is recommended

Table 3: Question 2 - With ovarian suppression will you opt for?

Options (%)	Tamoxifen	AI
Percentage of polled oncologists	0	100

Expert group consensus: Ovarian suppression is recommended using AI. AI=Aromatase inhibitor

Table 4: Question 3 - In hormone receptor negative patient, will you opt for luteinizing hormone-releasing hormone agonist for fertility preservation?

Options (%)	Yes	No
Percentage of polled oncologists	50	50

Expert group consensus: LHRH agonists is a valid option for fertility preservation in HR negative patients with early breast cancer. LHRH=Luteinizing hormone-releasing hormone, HR=Hormone receptor

Table 5: Question 4 - How do we monitor the postmenopausal status?

Expert group consensus: Postmenopausal status by hormonal evaluation should be monitored at baseline and at regular intervals on follow-up as surrogate marker for efficacy of the treatment

Table 6: Question 5 - Will the number of nodes involved influence your decision?

Expert group consensus: Yes

Table 7: Question 6 - For node negative cases, your choice will be?

Expert group consensus: Node negative high risk patients should receive ovarian suppression

likely to be achieved in very young women. International consensus guidelines for breast cancer management in young women suggested that the addition of a gonadotropin-releasing hormone (GnRH) agonist to tamoxifen be discussed on an individualized basis.[25]

In 2003, the International Breast Cancer Study Group (IBCSG) initiated two randomized, phase 3 trials, the Suppression of Ovarian FunctionTrial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), involving premenopausal women with hormone-receptor–positive early breast cancer.[11,12,26] SOFT was designed to determine the value of adding ovarian suppression to tamoxifen and to determine the role of adjuvant therapy with the aromatase inhibitor exemestane plus ovarian suppression in premenopausal women.

In SOFT, adding ovarian function suppression (OFS) to tamoxifen did not significantly improve disease-free survival versus tamoxifen alone in the overall population.[11] However, the addition of OFS improved disease outcomes in women at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal thereafter.

The effect of OFS on patient-reported outcomes in patients who received adjuvant tamoxifen was investigated in the Zoladex in Premenopausal Patients (ZIPP)[27,28] and the Eastern Cooperative Oncology Group E-3193[29] trials. Results indicate a greater detrimental effect on menopausal symptoms and sexual activity during treatment with OFS compared with tamoxifen alone.[27-29] In E-3193, overall QoL was worse when OFS was added to tamoxifen compared with tamoxifen alone at 3 years, with subsequent lessening of differences.[29]

While results from adjuvant endocrine therapy for postmenopausal women have recently improved through the use of aromatase inhibitors (AIs), this type of treatment continues to be a major clinical dilemma for premenopausal patients. Postmenopausal women with endocrine responsive disease are offered, at various times after surgery, with or without chemotherapy, a choice of endocrine therapies with either tamoxifen[30,31] or an AI.

The latter has been tested in postmenopausal women either after surgery,[32] after 2 to 3 years of tamoxifen to complete standard duration of this drug,[33] or after 5 years of tamoxifen to further reduce the risk of relapse, especially for patients at high risk of recurrence (ie, node-positive disease).[34]

There are several open questions that must be considered when experts discuss on the data ovarian suppression as adjuvant treatment for premenopausal patients. These include the type and duration of ovarian function suppression as well as the best way for it to be combined with other types of endocrine therapies, including selective estrogen receptor modulators (SERMs), AIs, and selective estrogen receptor down regulators (SERDs). In fact, data on the essence and extent of endocrine effects of chemotherapy are scant and the specific roles of both ovarian function suppression and of chemotherapy remain uncertain.

Ovarian Function Suppression/Ablation

Ovarian Suppression was the first form of systemic treatment for advanced breast cancer.[35] Its use as an adjuvant therapy was suggested several decades later, and the first randomized trials of ovarian ablation in the adjuvant setting began in 1948. A meta-analysis of these early trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has unequivocally established that ovarian ablation as a single intervention, whether induced by surgery or radiotherapy, is associated with significant improvement in recurrence-free and overall survival (OS) among women less than 50 years of age at the time of treatment.[7]

Surgical Oophorectomy

Surgical oophorectomy was the first form of ovarian ablation tested. It causes an immediate and permanent drop in ovarian steroid production. Current methods of laparoscopic surgery have dramatically reduced operative morbidity and mortality. Salpingo-Oophorectomy is assumed also to reduce the risk of ovarian cancer in women who are carriers of predisposition genes.[36,37]

Radiation-Induced Ovarian Suppression

Radiation-induced ovarian suppression is performed using several treatment algorithms, ranging from 4.5 Gy in one fraction to 10 to 20 Gy over five to six fractions. Radiation-induced ovarian ablation is a safe and simple outpatient approach, but it may be incomplete or significantly delayed in some women.[36] Biochemical verification of ovarian function cessation is thus required.

Gonadotropin Hormone-Releasing Hormone Analogs

Time-limited ovarian function suppression can be achieved with luteinizing hormone- or gonadotropin hormone-releasing hormone (LHRH or GnRH) agonists. LHRH agonists have been used during the past 25 years and are safe and reversible with no permanent ovarian dysfunction and with a side effect profile related to menopausal estrogen deprivation symptoms.[36,38]

The response rate with goserelin was similar to that of oophorectomy in patients with metastatic breast cancer.[38] There is no convincing comparison among the three forms of ovarian function suppression/ablation, and the current preferred use of GnRHanalogs is due to their reversible action. Hence, duration of treatment is potentially most critical in decision making.[39]

Chemotherapy

Cytotoxic chemotherapy represents a fourth form of ovarian suppression because of its capacity to cause temporary or permanent ovarian dysfunction in premenopausal women. Chemotherapy has been the mainstay of adjuvant therapy for premenopausal women with node-positive disease since the first trials of combination chemotherapy demonstrated significant benefits, especially for the younger cohort.[40,41] The use of chemotherapy was not considered a reasonable option for the minimal- or low-risk group of patients, despite available information on the efficacy of adjuvant chemotherapy, mainly in premenopausal patients.[42] How much of this benefit is due to the endocrine effects of chemotherapy is still a matter for research.[22,43]

It has been argued that cytotoxic chemotherapy is beneficial for premenopausal women with breast cancer because it causes premature menopause. Studies to date have not resolved the issue, although evidence appears to support the hypothesis of a dual mechanism of action of chemotherapy in this patient population: direct cytotoxicity and ovarian suppression resulting from chemotherapy-induced ovarian failure.[44]

Although the meta-analysis demonstrating a highly clinically significant benefit of ovarian ablation mainly compared the roles of radiation-induced and surgery-induced castration versus control not involving ovarian ablation, there is no scientific reason why chemotherapy-induced ovarian failure would not confer benefit, particularly in patients with hormone receptor–positive disease.[7]

Other Endocrine Therapies- AIs

Estrogens have a crucial role in breast cancer. Estradiol is biosynthesized from androgens by the enzyme complex called aromatase. Inhibition of aromatase is an important approach for reducing growth stimulatory effects of estrogensin estrogen-dependent breast cancer. Both steroidal and nonsteroidal AIs have shown clinical efficacy for the treatment of postmenopausal breast cancer.[45]

Treatment with AIs in premenopausal women together with GnRH analogs is obviously potentially effective. The combined use of goserelin and anastrozole as second-line endocrine therapy following progression on goserelin and tamoxifen produced significant clinical responses of worthwhile duration, with demonstrable endocrine changes, in premenopausal women (n = 16) with advanced breast cancer.[46]

Today, virtually all premenopausal women with lymph-node–positive, steroid hormone receptor–positive disease receive chemotherapy, despite the absence of evidence showing that it is necessary for all such women. Endocrine therapy alone, with ovarian function suppression and tamoxifen or an AI, may be sufficient to achieve excellent outcomes without chemotherapy, especially for patients at low risk of recurrent disease.[47]

Tamoxifen

The EBCTCG updated its overview analysis of tamoxifen trials in 1995 and results were available in the 1998 report.[48] Among women with ER-positive tumors, when the data were analyzed by age and duration of tamoxifen therapy, the trials in which tamoxifen was given for 5 years to women younger than 50 years revealed proportional risk reductions of 45% in recurrence and 32% in mortality. Unfortunately, EBCTCG analyses of tamoxifen conducted in 1990 and reported in 1992 showed only a modest effect of tamoxifen on recurrence and no effect on mortality for women below the age of 50 years.[49] This analysis of the tamoxifen effect was conducted across the board without considering the role of ER status of the primary and combining results of trials with various durations of tamoxifen and with and without chemotherapy.[50] Tamoxifen is associated with a variety of side effects including increased risk for endometrial cancer and thromboembolic disorders.[51] Investigations of bone mineral density in patients treated with prolonged tamoxifen have reported a possible decrease of density in premenopausal women.[52]

Combining Biological Compounds with Endocrine Agents

Most traditional cancer treatment regimens are generally nonselective, inducing cytotoxicity in normal as well as in malignant cells. In developing novel anticancer agents, the goal is to target specific molecular lesions within tumor cells (eg, HER-2), leading to improved cure rates and reducing cytotoxicity in normal cells.[53] Advances in the understanding of tumor pathobiology and molecular biology have allowed the development of targeted therapies.[54] The human epidermal growth factor receptor family of receptors is considered an important therapeutic target, and various types of small molecules, including monoclonal antibodies, protein tyrosine

kinase inhibitors, and vaccines are in development as potential therapies for metastatic breast cancer.[54,55]

Conclusion

For women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of ovarian suppression improved disease outcomes. We conclude that for premenopausal women with hormone-receptor–positive breast cancer, adjuvant treatment with ovarian suppression plus the aromatase inhibitor exemestane, as compared to ovarian suppression plus tamoxifen, provides a new treatment option that reduces the risk of recurrence.

Take Home Message

Case - 38 year old premenopausal lady diagnosed with infiltrating duct carcinoma left breast. She undergoes modified radical mastectomy. HPE results – T2N1M0. ER+ve, PR+ve, HER2NEU - ve. After adjuvant chemotherapy followed she needs hormonal therapy?

1. Ovarian suppression is recommended using Aromatase inhibitor
2. In HR negative patient, use of LHRHa for fertility preservation is an option
3. Post menopausal status should be monitored at baseline and at regular intervals on follow-up as surrogate marker for efficacy of the treatment.
4. Ovarian suppression should be used on all node positive patients. For node negative cases, ovarian suppression is recommended only for high risk patients.
5. Ovarian suppression plus the aromatase inhibitor exemestane (as compared with ovarian suppression plus tamoxifen) provides a new treatment option that has the potential to reduce the risk of recurrence.

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Conflicts of interest

There are no conflicts of interest.

References

1. Jemal A, Thomas A, Murray T, Thun M. Cancer statistics, 2002. CA Cancer J Clin 2002;52:23-47.
2. Goldhirsch A, Gelber RD. Breast cancer in young women. In: Harris JR, Lippman ME, Morrow M, editors. Diseases of the Breast. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2004. p. 1339-49.
3. Kalantaridou SN, Davis SR, Nelson LM. Premature ovarian failure. Endocrinol Metab Clin North Am 1998;27:989-1006.
4. Morimoto T, Okazaki M, Endo T. Current status and goals of mammographic screening for breast cancer in japan. Breast Cancer 2004;11:73-81.
5. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment with illustrative cases. Lancet 1896;2:104-7.
6. Paterson R, Russel MH. Clinical trials in malignant disease. Part II-breast cancer: Value of irradiation of the ovaries. J Fac Radiol 1959;10:130-3.
7. Ovarian ablation in early breast cancer: Overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1996;348:1189-96.
8. Kohler BA, Sherman RL, Howlader N, Jemal A, Ryerson AB, Henry KA, *et al.* Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/Ethnicity, poverty, and state. J Natl Cancer Inst 2015;107:djv048.
9. 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.
10. 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;381:805-16.
11. Francis PA, Regan MM, Fleming GF, Láng I, Ciruelos E, Bellet M, *et al.* Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015;372:436-46.
12. Pagani O, Regan MM, Walley BA, Fleming GF, Colleoni M, Láng I, *et al.* Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 2014;371:107-18.
13. National Cancer Registry Programme, Indian Council of Medical Research. Leading sites of cancer. In: Consolidated Report of Population Based Cancer Registries 2001-2004, Incidence and Distribution of Cancer. Bangalore: Coordinating Unit, National Cancer Registry Programme (ICMR); 2006. p. 8-30.
14. Badwe RA, Gangawal S, Mittra I, Desai PB. Clinico-pathological features and prognosis of breast cancer in different religious communities in India. Indian J Cancer 1990;27:220-8.
15. Altekruse SF, Kosary CL, Krapcho M, editors. In: SEER Cancer Statistics Review. National Cancer Institute; 1975-2007.
16. National Cancer Registry Program. Ten Year Consolidated Report of the Hospital Based Cancer Registries, 1984–1993, an Assessment of the Burden and Care of Cancer Patients. New Delhi: Indian Council of Medical Research; 2001.
17. Agarwal G, Pradeep PV, Aggarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. World J Surg 2007;31:1031-40.
18. Eifel P, Axelson JA, Costa J, Crowley J, Curran WJ Jr. Deshler A, *et al.* National institutes of health consensus development conference statement: Adjuvant therapy for breast cancer, November 1-3, 2000. J Natl Cancer Inst 2001;93:979-89.
19. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Senn HJ. Meeting highlights: International consensus panel on the treatment of primary breast cancer. Seventh international conference on adjuvant therapy of primary breast cancer. J Clin Oncol 2001;19:3817-27.
20. LHRH-agonists in Early Breast Cancer Overview Group, Cuzick J, Ambroisine L, Davidson N, Jakesz R, Kaufmann 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.
21. Griggs JJ, Somerfield MR, Anderson H, Henry NL, Hudis CA, Khatcheressian JL, *et al.* American Society of Clinical Oncology endorsement of the cancer care Ontario practice guideline on adjuvant ovarian ablation in the treatment of premenopausal women with early-stage invasive breast cancer. J Clin Oncol 2011;29:3939-42. In Erratum, J Clin Oncol 2012;30:1398.
22. Pagani O, O'Neill A, Castiglione M, Gelber RD, Goldhirsch A, Rudenstam CM, *et al.* Prognostic impact of amenorrhoea after adjuvant chemotherapy in premenopausal breast cancer patients with axillary node involvement: Results of the International Breast Cancer Study Group (IBCSG) trial VI. Eur J Cancer 1998;34:632-40.
23. International Breast Cancer Study Group, Colleoni M, Gelber S, Goldhirsch A, Aebi S, Castiglione-Gertsch M, *et al.* Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: International Breast Cancer Study Group trial 13-93. J Clin Oncol 2006;24:1332-41.
24. Swain SM, Jeong JH, Wolmark N. Amenorrhea from breast cancer therapy – not a matter of dose. N Engl J Med 2010;363:2268-70.
25. Partridge AH, Pagani O, Abulkhair O, Aebi S, Amant F, Azim HA Jr., *et al.* First international consensus guidelines for breast cancer in young women (BCY1). Breast 2014;23:209-20.
26. Regan MM, Pagani O, Fleming GF, Walley BA, Price KN, Rabaglio M, *et al.* Adjuvant treatment of premenopausal women with endocrine-responsive early breast cancer: Design of the TEXT and SOFT trials. Breast 2013;22:1094-100.
27. Nystedt M, Berglund G, Bolund C, Fornander T, Rutqvist LE. Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: A prospective randomized study. J Clin Oncol 2003;21:1836-44.
28. Berglund G, Nystedt M, Bolund C, Sjödén PO, Rutquist LE. Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: A prospective randomized study. J Clin Oncol 2001;19:2788-96.
29. Tevaarwerk AJ, Wang M, Zhao F, Fetting JH, Cella D, Wagner LI, *et al.* Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): A trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2014;32:3948-58.
30. Tamoxifen for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351:1451-67.
31. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ,

et al. Meeting highlights: Updated international expert consensus on the primary therapy of early breast cancer. J Clin Oncol 2003;21:3357-65.
32. Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, Howell A, *et al.* Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. Cancer 2003;98:1802-10.
33. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, *et al.* A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081-92.
34. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, *et al.* A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793-802.
35. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment. Lancet 1896;2:104-7, 162-5.
36. Davidson NE. Ovarian ablation as adjuvant therapy for breast cancer. J Natl Cancer Inst Monogr 2001;67-71.
37. Calderon-Margalit R, Paltiel O. Prevention of breast cancer in women who carry BRCA1 or BRCA2 mutations: A critical review of the literature. Int J Cancer 2004;112:357-64.
38. Boccardo F, Rubagotti A, Perrotta A, Amoroso D, Balestrero M, De Matteis A, *et al.* Ovarian ablation versus goserelin with or without tamoxifen in pre-perimenopausal patients with advanced breast cancer: Results of a multicentric Italian study. Ann Oncol 1994;5:337-42.
39. Taylor CW, Green S, Dalton WS, Martino S, Rector D, Ingle JN, *et al.* Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: An intergroup study. J Clin Oncol 1998;16:994-9.
40. Fisher B, Carbone P, Economou SG, Frelick R, Glass A, Lerner H, *et al.* 1-phenylalanine mustard (L-PAM) in the management of primary breast cancer. A report of early findings. N Engl J Med 1975;292:117-22.
41. Bonadonna G, Brusamolino E, Valagussa P, Rossi A, Brugnatelli L, Brambilla C, *et al.* Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976;294:405-10.
42. Fisher B, Dignam J, Tan-Chiu E, Anderson S, Fisher ER, Wittliff JL, *et al.* Prognosis and treatment of patients with breast tumors of one centimeter or less and negative axillary lymph nodes. J Natl Cancer Inst 2001;93:112-20.
43. Mehta RR, Beattie CW, Das Gupta TK. Endocrine profile in breast cancer patients receiving chemotherapy. Breast Cancer Res Treat 1992;20:125-32.
44. Pater JL, Parulekar WR. Ovarian ablation as adjuvant therapy for premenopausal women with breast cancer – Another step forward. J Natl Cancer Inst 2003;95:1811-2.
45. Brueggemeier RW. Aromatase inhibitors: New endocrine treatment of breast cancer. Semin Reprod Med 2004;22:31-43.
46. Forward DP, Cheung KL, Jackson L, Robertson JF. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. Br J Cancer 2004;90:590-4.
47. International Breast Cancer Study Group. Randomized controlled trial of ovarian function suppression plus tamoxifen versus the same endocrine therapy plus chemotherapy: Is chemotherapy necessary for premenopausal women with node-positive, endocrine responsive breast cancer? First results of International Breast Cancer Study Group Trial 11-93. Breast 2001;10 Suppl 3:130-8.
48. Tamoxifen for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;351:1451-67.
49. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. Lancet 1992;339:1-5.
50. Gelber RD, Goldhirsch A, Coates AS. Adjuvant therapy for breast cancer: Understanding the overview. International Breast Cancer Study Group. J Clin Oncol 1993;11:580-5.
51. Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S, *et al.* Overview of the main outcomes in breast-cancer prevention trials. Lancet 2003;361:296-300.
52. Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premenopausal and postmenopausal women. J Clin Oncol 1996;14:78-84.
53. Nahta R, Esteva FJ. HER-2-targeted therapy: Lessons learned and future directions. Clin Cancer Res 2003;9:5078-84.
54. Esteva FJ. Monoclonal antibodies, small molecules, and vaccines in the treatment of breast cancer. Oncologist 2004;9 Suppl 3:4-9.
55. Noonberg SB, Benz CC. Tyrosine kinase inhibitors targeted to the epidermal growth factor receptor subfamily: Role as anticancer agents. Drugs 2000;59:753-67.