Review

Endocrinology and hormone therapy in breast cancer

Endocrine therapy in premenopausal women

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Abstract

Endocrine therapy remains important in premenopausal women with hormone receptor positive breast cancer. Ovarian ablation, used alone, is effective in delaying recurrence and increasing survival in such women. When added to chemotherapy, it is less clear that it is effective perhaps because of the endocrine ablative effect of chemotherapy. Trials comparing ovarian ablation with or without tamoxifen to CMF-type chemotherapy suggest that the endocrine therapy is equivalent to or better than this chemotherapy in women whose tumors have estrogen and/or progesterone receptor. Tamoxifen is also effective in preventing recurrence and prolonging survival in the adjuvant setting in premenopausal women. While most of the available data deals with tamoxifen given alone, it appears to have a similar beneficial effect when added to chemotherapy in the premenopausal adjuvant setting. Adjuvant aromatase inhibitors should not be used in premenopausal women.

Introduction

Endocrine therapy, developed over a century ago [1,2], remains the most effective and the most clearly targeted form of systemic therapy for breast cancer. Endocrine treatments work best in women whose tumours are positive for oestrogen receptor (ER) and/or progesterone receptor (PgR). As we continue to search for newer targeted therapies that will shrink cancers effectively with few undesired side effects, and carry out complex statistical analyses to identify predictive factors, we should not forget the first targeted cancer therapy, namely ovarian ablation (OA) for breast cancer, and the first predictive factor for treatment of any cancer, the ER.

Premenopausal adjuvant endocrine therapy

Ovarian ablation

For many years adjuvant OA was used and felt to be helpful, but randomized trials were not done. Subsequently, a few small randomized trials were conducted in the 1960s and 1970s. Before the first Early Breast Cancer Trialists Collaborative Group (EBCTCG) or Oxford overview was published in 1984 [3], it was generally believed that these trials showed no benefit for OA. When the meta-analytic techniques used in the EBCTCG overview were applied to these small trials, however, it became apparent that OA was associated with a reasonably large positive effect on both disease-free survival (DFS) and overall survival (OS) in node-positive and node-negative premenopausal women [3–5].

The most recent EBCTCG overview (www.ctsu.ox.ac.uk/ebctcg/), carried out in September 2000, included updated information on 4900 women aged under 50 years included in 15 trials of OA. Only about 1300 of these women were in trials of OA in the absence of chemotherapy, whereas more than 3500 were in trials of OA in the presence of chemotherapy. In this updated analysis there was a clear separation between the trials of OA versus no treatment in the absence of chemotherapy and trials of OA plus chemotherapy versus the same chemotherapy. In the former trials large and highly significant positive effects of OA persisted at 15 years in terms of recurrence (59.0% versus 45.6%; difference = 13.4%, standard error [SE] = 3.2), breast cancer deaths (59.4 versus 49.1%; difference = 10.3%, SE = 3.1), and all deaths (56.7% versus 46.3%; difference = 10.4%, SE = 3.1). In contrast, the trials of OA plus chemotherapy versus the same chemotherapy found no significant difference in terms of recurrence (52.5% versus 55.8%; difference = –3.2%, SE = 3.6), breast cancer deaths (47.1% versus 52.4%; difference = –5.3%, SE = 3.3), or all deaths (46.6 versus 52.1%; difference = –5.5%, SE = 3.3).

AC = doxorubicin and cyclophosphamide; CAF = cyclophosphamide, doxorubicin and 5-fluorouracil; CEF = cyclophosphamide, epirubicin and 5-fluorouracil; CMF = cyclophosphamide, methotrexate and 5-fluorouracil; DFS = disease-free survival; EBCTCG = Early Breast Cancer Trialists Collaborative Group; ER = oestrogen receptor; FAC = 5-fluorouracil, doxorubicin and cyclophosphamide; FEC = 5-fluorouracil, epirubicin and cyclophosphamide; LHRH = luteinizing hormone-releasing hormone; OA = ovarian ablation; OS = overall survival; PgR = progesterone receptor; RR = relative risk; SE = standard error.

One randomized trial from Scotland [6], conducted in premenopausal node-positive and node-negative women, compared intravenous cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy given every 3 weeks for eight cycles versus ovarian removal. There was no significant difference between the effects of CMF and those of ovarian removal on either DFS or OS. Those with ER levels greater than 100 fmol/mg, however, had better DFS and OS with ovarian removal, whereas those with ER levels of under 100 fmol/mg did better with CMF. Although this CMF chemotherapy schedule is known to be less effective than standard Bonnadonna day 1 and 8 CMF (cyclophosphamide 100 mg/m^2 on days 1–14, and methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2 each given on days 1 and 8, intravenously) [7], that study does suggest that ovarian removal in women with high levels of ER may be as effective or more effective than at least some types of CMF chemotherapy.

Few other studies of this design were done until recently. An as yet unpublished trial by Ejlertsen and coworkers [8] was presented at the 1999 Meeting of the American Society of Clinical Oncology. In that trial 732 premenopausal women, who had ER-positive tumours that were either node positive and/or whose tumour size was greater than 5 cm, were randomly assigned to receive OA by radiation therapy or CMF intravenously for nine cycles. DFS at 5 years was superior for OA, but OS was equivalent. We await full publication of these study results.

Luteinizing hormone-releasing hormone analogues

More recently, the development of the luteinizing hormone-releasing hormone (LHRH) analogues has re-awakened interest in the use of OA. In one relatively large phase III trial [9] the LHRH analogue goserelin (Zoladex; AstraZeneca Canada Inc., Mississauga, Ontario, Canada) was shown to be as effective as surgical OA in the treatment of metastatic breast cancer. Recently, four small studies comparing tamoxifen plus an LHRH analogue versus an LHRH analogue alone suggested that the combination may be superior in terms of progression and OS in the metastatic setting [10]. This suggests that the combination of an LHRH analogue and tamoxifen might confer additional benefit over either alone in the adjuvant setting. Various LHRH analogues (in particular Zoladex) have now been tested in adjuvant therapy using study designs that compare Zoladex, tamoxifen, or Zoladex plus tamoxifen versus chemotherapy in the premenopausal setting, or that add Zoladex, tamoxifen, or Zoladex plus tamoxifen to chemotherapy in the same group of women.

In one trial conducted by Jakesz and coworkers [11] 1095 women with stage I and II, ER-positive and/or PgR-positive breast cancer were randomly assigned to receive Zoladex plus tamoxifen or CMF chemotherapy. Women receiving the endocrine therapy had significantly improved DFS ($P < 0.02$) but OS was not significantly different between treatments. In another landmark study, the ZEBRA (Zoladex Early Breast Cancer Research Association) trial, conducted by Jonat and coworkers [12], 1640 premenopausal and perimenopausal node-positive women whose tumours were ER positive or negative were randomly assigned to receive Zoladex for 2 years or CMF for six cycles. In ER-positive women DFS and OS were equivalent, whereas in ER-negative women DFS and OS were superior in the CMF arm. In both of those trials, women who became amenorrhoeic following CMF therapy had better outcomes than those who did not, suggesting that the endocrine effects of chemotherapy also play a role in this setting.

Rutqvist [13] has reported but not fully published results from the Zoladex in Premenopausal Patients trial – a large randomized 2 × 2 factorial study in which premenopausal women with early-stage disease were randomly assigned, after primary surgery, to receive one of the following treatments: tamoxifen for 2 years; Zoladex (26 monthly subcutaneous injections); tamoxifen plus Zoladex; and no endocrine therapy. Some patients electively received tamoxifen, or not and were randomly assigned to just Zoladex. The study protocol also permitted the use of elective adjuvant chemotherapy. A total of 2631 women, of whom 56% were node negative, were included. Information regarding ER status was available in 1577 (60%) of the women. At a median follow up of 4.3 years, fewer recurrences (261 [20%]) were observed among patients assigned to Zoladex than among those who did not receive Zoladex (330 [24.9%]; relative hazard = 0.77, 95% confidence interval = 0.66–0.90; $P = 0.001$). This effect was most pronounced among those who were known to have ER positive disease. The benefit with Zoladex appeared to be somewhat less among those who received concurrent adjuvant tamoxifen or adjuvant chemotherapy, but the differences compared with patients who did not receive such concurrent treatments were not statistically significant. There were also fewer deaths in the women allocated to receive Zoladex, although this finding was not statistically significant (140 [10.7%] versus 165 [12.4%]; relative hazard = 0.84, 95% confidence interval = 0.67–1.05; $P = 0.12$). Thus, in that study medical castration with Zoladex for 2 years in premenopausal ER-positive patients produced a statistically significant benefit in terms of DFS, and a trend toward improvement in OS, irrespective of concurrent adjuvant tamoxifen or chemotherapy.

Several other randomized trials [8,14,15] compared CMF versus ovarian suppression with or without tamoxifen, and two compared FAC (5-fluorouracil, doxorubicin and cyclophosphamide) or FEC (5-fluorouracil, epirubicin and cyclophosphamide) versus ovarian suppression plus tamoxifen, all with similar results suggesting equivalence or

Table 1

Chemotherapy versus ovarian suppression

Study	Treatments	Results
Scottish [6]	CMF versus surgery	No difference
Scandinavian [8]	CMF versus XRT	No difference
ZEBRA [12]	CMF versus OS	No difference for ER+
IBCSG VIII	CMF versus OS	No difference for ER+
GROCTA 02 [47]	CMF versus OS + tamoxifen	No difference
ABCSG 5 [11]	CMF versus OS + tamoxifen	Better RFS for OS + tamoxifen
French	FAC versus OS + tamoxifen	No difference
FASG 06 [48]	FEC versus OS + tamoxifen	No difference
GABG IVA–93 [14]	CMF versus goserelin	No difference
Wallwiener and coworkers[15]	CMF versus leuprolin	No difference

CMF, cyclophosphamide, methotrexate and 5-fluorouracil; ER, oestrogen receptor; FAC, 5-fluorouracil, doxorubicin and cyclophosphamide; FEC, 5-fluorouracil, epirubicin and cyclophosphamide; OS, ovarian suppression; XRT, radiotherapy.

superiority for the endocrine arm (Table 1). However, with the development of second- and third-generation combinations such as cyclophosphamide, epirubicin and 5-fluorouracil (CEF), which is more efficacious than standard Bonadonna CMF [16], and doxorubicin and cyclophosphamide (AC) taxol, which produces better results than AC alone [17], it is unclear what final conclusions one should draw from studies that compare 'first-generation' chemotherapy regimens such as AC or CMF versus OA by whatever means [18].

The results of another interesting study from the Eastern Cooperative Oncology Group were presented by Davidson [19] at the 1999 Meeting of the American Society of Clinical Oncology. That study compared cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) versus CAF plus Zoladex or CAF plus Zoladex and tamoxifen in 1504 premenopausal node-positive women. It showed that the addition of tamoxifen to CAF plus Zoladex was significantly better in terms of DFS ($P = 0.01$) but not OS. The addition of Zoladex to CAF resulted only in a trend toward improvement in DFS ($P = 0.10$). A preliminary, hypothesis-generating analysis presented by Davidson suggested that the addition of Zoladex was more effective in younger women and/or in women who did not become postmenopausal as a result of chemotherapy, whereas the addition of tamoxifen seemed more effective in older women and/or in women who became menopausal as a result of their chemotherapy. This hypothesis remains to be further explored and substantiated in prospective randomized trials designed to address this issue.

In the most recent Oxford overview in September 2000 (www.ctsu.ox.ac.uk/ebctcg/), five trials of the LHRH agonist Zoladex versus not, in 5700 women were identified. Data on only three of these trials, including 4200 women, were available. In the Eastern Cooperative Oncology Group trial [19] all patients had received CAF chemotherapy; in the FCNLCC (Fédération Nationale des Centres de Lutte contre le Cancer) French trial, all women received chemotherapy before being randomly assigned to Zoladex or control; and in the ZIPP trial 1173 out of 2710 women had received elective chemotherapy before randomization to Zoladex and/or tamoxifen [13]. The 2000 overview has not yet analyzed these trials by dividing patients into those who received concurrent chemotherapy and those who did not. However, with about 5 years of follow up it seems that, overall, goserelin is associated with significant reduction in recurrence (73% versus 68.6%; difference = 4.4%, SE = 1.6), whereas breast cancer deaths and all deaths show only a trend toward improvement with goserelin (breast cancer deaths: 86.2% versus 84.1%; difference = 2.1%, SE = 1.2; all deaths: 85.9% versus 83.9%; difference = 2.0%, SE = 1.2).

It seems that further trials with much larger numbers of women and events are required. Furthermore, ongoing analyses in the EBCTCG process of the effects of OA by whatever means, with women clearly divided into those who have and those who have not received concurrent chemotherapy, are needed. It is also important to examine women receiving chemotherapy who have become amenorrhoeic in comparison with those who have not. Is the addition of OA by whatever method perhaps important only in those women who do not achieve amenorrhoea following chemotherapy? Prospective randomized trials of this specific question are currently being considered by groups around the world (Goldhirsch A, personal

communication). In particular, the Suppression of Ovarian Function Trial (SOFT) will determine whether OA confers additional benefit in women who have received current standard chemotherapy but have not become amenorrhoeic. This International Breast Cancer Trials Group trial is now accruing patients actively, with cooperative participation from the North American Intergroup and others. The International Breast Cancer Trials Group has also designed two other trials, which, together with SOFT, form a suite or group of nested trials. In the first of these trials, the Tamoxifen/Exemestane Trial (TEXT), premenopausal women who undergo OA by any means are being randomly assigned to receive either tamoxifen or exemestane; the trial will test whether tamoxifen or an aromatase inhibitor is better once premenopausal women are made postmenopausal. In the second trial, the Premenopausal Endocrine-Responsive Chemotherapy Trial (PERCHE), women who have received OA and tamoxifen or OA and exemestane are being randomly assigned to receive chemotherapy or no chemotherapy. PERCHE will test the concept of whether chemotherapy confers additional benefit to optimal adjuvant endocrine therapy in premenopausal women.

Tamoxifen

After tamoxifen was studied in metastatic disease in postmenopausal [20] and premenopausal women [21], it was then tested as adjuvant therapy in both postmenopausal and premenopausal women. The earliest randomized controlled studies [22–26] were conducted mainly in postmenopausal node-positive women. Subsequent studies [27], however, showed that tamoxifen used alone was also effective in premenopausal and postmenopausal node-negative women, producing positive effects on DFS and OS that were similar in magnitude to those of chemotherapy in this setting. The first EBCTCG overview [3] clarified the presence of strong and consistent improvements in women receiving tamoxifen, particularly those who were postmenopausal and ER positive. In the early overview analyses, however, relatively small numbers of premenopausal women were randomized in trials of tamoxifen, and most trials were of 1–2 years of therapy. The results of subsequent trials with 5 years of tamoxifen therapy have clarified the magnitude of the benefit from tamoxifen. In the most recent EBCTCG tamoxifen overview [28], it was clearly demonstrated that premenopausal women randomly assigned to receive 5 years of tamoxifen versus no systemic therapy had substantial DFS and OS benefits. More of the women in these later trials were selected to be ER and/or PgR positive, which probably also increased the magnitude of the effect seen with tamoxifen.

Within the premenopausal group, however, there are still few data concerning women randomly assigned to receive chemotherapy or chemotherapy plus tamoxifen. Only 205 such women were included in the most recent Oxford overview, of whom only 177 were ER positive (Peto R, personal communication) [29]. In this group of women in the overview, there was a marginally significant improvement in DFS and a trend toward improvement in OS but, because of the relatively small numbers of women studied, the effects in this subgroup are less certain.

Subsequent to the 1995 Oxford overview, a Danish trial [30] was published in which 634 premenopausal women were randomly assigned to receive either tamoxifen 20 mg/day for one year concurrent with CMF, or no tamoxifen. That study found no benefit overall from the addition of tamoxifen. This may relate to the short duration of tamoxifen treatment, because 2 or 5 years is now believed to be more efficacious, at least in other settings. However, in this trial there was a nonsignificant trend for receptor-positive women to benefit from tamoxifen and for receptor-negative women to do more poorly if given tamoxifen, in terms of both DFS and OS. The Southwest Oncology Group also recently reported the results of a large randomized study [31] in which high-risk, node-negative, premenopausal and postmenopausal women were randomly assigned to receive 5 years of tamoxifen or no further therapy following randomization to receive chemotherapy with either CAF or CMF. Tamoxifen was given subsequent to chemotherapy. The data showed that only receptor positive postmenopausal women achieved significant benefit from the addition of tamoxifen.

At least three additional trials in which premenopausal women are randomly assigned to receive chemotherapy or chemotherapy followed by tamoxifen are currently ongoing or have recently been completed [32,33] (Bramwell V, personal communication). In the International Breast Cancer Study Group 13-93 trial [32], premenopausal women not considered suitable for endocrine therapy alone were randomly assigned to receive either AC for four cycles followed immediately by CMF for three cycles, or AC for four cycles followed by a gap and then CMF for three cycles; and in a cross randomization to tamoxifen for 5 years beginning after chemotherapy, or no tamoxifen. Five-year DFS was significantly improved (72% versus 64%, relative risk [RR] = 0.76; $P < 0.005$) for tamoxifen in the entire group of patients and in those who were ER positive (75% versus 63%, RR = 0.61; $P < 0.0001$), but not in women whose tumours were ER low (67% versus 59%, RR = 085; $P = 0.29$) or absent (62% versus 81%, RR = 1.95; $P = 0.07$). This trial suggests that adding tamoxifen in women with ER positive disease is beneficial, but that adding it in women with ER negative disease, may be detrimental.

Also recently reported was the European Organisation for Research and Treament of Cancer 01901 trial in premenopausal women with node-positive and node-negative

disease, who were randomly assigned, following chemotherapy with CMF, FAC, FEC, CAF, or CEF, to tamoxifen for 3 years or no tamoxifen [33]. The findings, presented at the 2004 European Conference on Clinical Oncology Meeting, indicate that for the entire group including premenopausal and postmenopausal women, tamoxifen was superior with respect to DFS but there was no difference in OS. The data have not yet been presented by menopausal status. The National Cancer Institute of Canada Clinical Trial Group MA.12 trial, which randomized women after receiving AC, CMF, or CEF to tamoxifen or placebo for 5 years, will undergo its first analysis early in 2005 (Bramwell V, personal communication).

In most parts of the world, certainly in North America, it has become common practice to follow adjuvant chemotherapy with tamoxifen in ER-positive or PgR-positive premenopausal women.

Summary

Optimal treatment for premenopausal women remains a subject for further study. Second-generation adjuvant chemotherapies such as CEF [16] and AC taxol [17] have probably become the treatments of choice for premenopausal women at high risk and/or with ER-negative and PgR-negative disease. However, there are now considerable data suggesting that OA by surgery, irradiation, or an LHRH analogue, with or without the addition of tamoxifen, may represent a viable alternative to at least first-generation chemotherapies such as CMF or AC in premenopausal women with ER-positive and/or PgR-positive early breast cancer and low or intermediate risk [18]. Tamoxifen used alone was also clearly shown to be effective as adjuvant therapy in node-negative and lower risk ER-positive and PgR-positive women, but there are virtually no data directly comparing its efficacy with that of chemotherapy or OA in the adjuvant setting. Although there are considerable preliminary data suggesting that adding OA and/or tamoxifen to adjuvant chemotherapy in premenopausal receptor positive women may add some small benefit, it is unclear how large such additional benefit may be or even whether a significant benefit may consistently be achieved. The relative benefit of such therapy in various subgroups also remains to be clarified.

Use of other predictive factors

Recently, a considerable body of reports has suggested that women treated with tamoxifen may respond less well if their tumours over-express neu/erb B-2 antigen. Although some studies support this contention [34–37], others do not [38–44]. Of even greater interest is that some studies have suggested that neu/erb B-2 over-expressing tumours may be more responsive to other endocrine agents such as aromatase inhibitors [34], but once again some analyses of this matter are contradictory [45]. In addition, the only trial examining the role of neu/erb B-2 in premenopausal women, that of Love and coworkers [46], suggests that patients whose tumours over-express neu/erb B-2 are more likely to respond to adjuvant treatment with OA and tamoxifen than are patients whose tumours do not over-express. Thus, it appears that over-expression of neu/erb B-2 should not be used as a predictive factor to select endocrine versus chemotherapy or for particular types of endocrine therapy at this time. Further studies of the role of neu/erb B-2 over-expression in order to explain and clarify these contradictory findings are urgently required. Hopefully, neu/erb B-2 over-expression and other molecular markers will be useful in the near future as we refine and target endocrine therapy toward the women who are most likely to benefit from it.

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Conclusion

Endocrine treatment remains important for women in the adjuvant setting. The exact combination and sequence of these drugs is still under investigation but more is known with each passing year. Randomized trials have greatly clarified the precise role of the more established of these endocrine agents, but, in addition, a variety of new agents are currently under development. These include the pure anti-oestrogens, such as Faslodex, and newer selective ER modulators such as raloxifene. Results of trials with these agents are awaited with great interest.

Competing interests

KP has been a consultant with Aventis, AstraZeneca, Roche, Pharmacia Inc., Ortho-Biotech, Pfizer, YM Biosciences and Biomira. KP has received research funding either directly through per case funding for studies, or indirectly through the National Cancer Institute of Canada Clinical Trials Group, contracted with pharmaceutical companies from Pharmacia Inc., AstraZeneca, Bristol Myers Squibb, Aventis, Amgen, Ortho-Biotech and Pfizer.

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