
To the Editor: We read with great interest the two articles and the editorial in the December 15, 2002 issue of the Journal of Clinical Oncology, concerning adjuvant hormonal treatment of breast cancer. In both studies, the authors compared a “standard” cyclophosphamide, methotrexate fluorouracil–(CMF–) only treatment arm with goserelin or goserelin plus tamoxifen. According to Jonat et al, goserelin offers an effective, well-tolerated alternative to CMF chemotherapy in the management of premenopausal patients with ER- [estrogen receptor–] positive and node-positive early breast cancer.” According to Jakesz et al, “complete endocrine blockade with goserelin and tamoxifen is superior to standard chemotherapy in premenopausal women with hormone-responsive stage I and II breast cancer.” In the editorial commenting on these two studies, Kathleen Pritchard asked, “Is it time for another paradigm shift?”

If this question is asked in the context of the previously mentioned studies, the answer might be, “Not yet.” Let us repeat what we all know. First, anthracycline-containing regimens yield superior results, both for recurrence-free survival (absolute difference at 5 years, 3.2%) and overall survival (absolute difference at 5 years, 2.7%). In both the Jonat et al and Jakesz et al studies, the control arm was patients receiving CMF. We know that 4 months of doxorubicin and cyclophosphamide is clearly equivalent to 6 months of CMF; however, we also know that there are regimens that are clearly superior to CMF6,7 that have been defined in previously reported studies.8

Second, tamoxifen was associated with a highly significant improvement in recurrence-free survival (absolute difference at 10 years, 14.9%–15.2%) and in overall survival (absolute difference at 10 years, 5.5%–10.9%) in ER-positive women. In the article by Jonat et al and in the accompanying editorial,9 it was acknowledged that there were only 177 women with ER-positive disease who were randomly selected to chemotherapy, or to chemotherapy plus tamoxifen in the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) overview. According to the Jonat et al and the accompanying editorial, although widely used in practice, not enough data were available to support the addition of tamoxifen after standard chemotherapy in premenopausal patients, and this argument was used as a justification for lack of tamoxifen use in the control groups. However, both in the recently published studies, as well as in all other studies cited in the editorial that compared ovarian ablation with chemotherapy (mostly with CMF), the chemotherapy plus tamoxifen regimen is apparently lacking. So “177” is better than “zero,” and as a general rule, absence of proof does not mean proof of absence. On the other side, Jakesz et al, in addressing the choice of treatment in the control arm, stated that when Austrian Breast and Colorectal Cancer Study Group Trial 5 was launched in 1990, the data of the EBCTCG overview were largely unknown; therefore, CMF only, the chemotherapeutic regimen of choice at that time, was chosen. However, knowing the data at present, we do not accept CMF without tamoxifen as a “standard” in this group, and so we cannot come to the same conclusion of Jakesz et al, who reported that “complete endocrine blockade with goserelin and tamoxifen is superior to standard chemotherapy in premenopausal woman with hormone responsive stage I and II breast cancer”. We still do not know what is the “best standard” chemotherapy for lymph node–positive, ER-positive premenopausal breast cancer; however, we absolutely know what is not. CMF without tamoxifen is clearly not a sufficient treatment in this group of patients. Studies with a control arm of anthracycline-based chemotherapy plus tamoxifen are definitely and urgently needed in order that the conclusions of Jakesz et al be better received.

After reading the results of these two trials, we draw a conclusion that is different from those reported. Ovarian ablation with goserelin is equivalent to CMF without tamoxifen, and goserelin plus tamoxifen is more effective than CMF without tamoxifen. If one has a premenopausal patient with ER-positive, lymph node–positive breast cancer, goserelin plus tamoxifen is a good alternative to treating her with intravenous CMF without tamoxifen while achieving the same results. Is there anyone who would treat such a patient with CMF only?

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REFERENCES


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Can Endocrine Treatment for Hormone-Positive Premenopausal Women With Early Breast Cancer Replace Adjuvant Chemotherapy?

To the Editor: In the December 15, 2002 issue of the Journal of Clinical Oncology, Jakesz et al1 and Jonat et al2 tried to determine the best
postoperative treatment for hormone-receptor–positive premenopausal women with early breast cancer. Jakesz et al showed that a complete endocrine blockade with 3 years of receiving goserelin and 5 years receiving tamoxifen was more effective than chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF). Relapse-free survival and local recurrence-free survival were significantly in favor of the endocrine therapy, and there was a trend in favor of the endocrine treatment for overall survival, but this was not statistically significant.

Jonat et al compared 2 years of receiving goserelin with adjuvant CMF therapy. Disease-free survival was identical for patients with estrogen-receptor–positive tumors.

Both studies were well performed, but neither group mentioned the overexpression of neuB2 overexpression in their series. They both used CMF chemotherapy as their control arm. While some studies have shown that neuB2 overexpression is associated with less benefit from CMF chemotherapy, the overexpression of neuB2 has also been shown to be associated with relative resistance to hormone therapies. There is, however, some discrepancy in other reports on the overexpression of this predictive marker and response to endocrine treatment. An uneven distribution of neuB2 overexpression might have influenced the outcomes of both studies.

Predictive markers such as neuB2 overexpression should be included in the analysis in order to optimize treatment for this group of patients. It can be concluded that optimal postoperative treatment of premenopausal hormone-receptor–positive patients will remain an open issue, and the treatment of choice is inclusion in large randomized trials.

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REFERENCES


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Combined Endocrine Blockade in Premenopausal Breast Cancer: A Superior Therapeutic Option for Adjuvant Management?

To the Editor: We read with interest the results of the Austrian Breast and Colorectal Cancer Study Group Trial 5, published in the December 15, 2002, issue of the Journal of Clinical Oncology. The authors compared adjuvant chemotherapy (CT) to adjuvant combination endocrine therapy (ET) in early-stage, premenopausal women and suggested that combined endocrine therapy (goserelin-tamoxifen) is significantly more effective in this patient population.

While the trial explores an important therapeutic issue, the authors’ conclusions are perhaps overreaching. An analysis of the results shows that of the total 197 relapses in both arms (88 in the ET arm; 109 in the CT arm), there were nine more contralateral breast cancer cases in the chemotherapy arm (12 in the CT arm versus three in the ET arm). There is likely a chemo-protective element of tamoxifen2 at work, which may be responsible for this reduction of contralateral breast tumors observed in the ET arm rather than a systemic treatment effect of the ET combination. If this were taken into account, we wonder whether the statistical difference in the number of relapses observed in the two arms (88 ET; 109 CT) would remain significant, as noted in the study at present (P = .03).

To this end, it may also be noted that neither the overall survival rates nor the numbers of distant relapses observed in both treatment arms were statistically different. Therefore, if patients receiving chemotherapy in this trial were also to have received tamoxifen (the use of which is now an accepted standard practice in similar patient populations at the conclusion of adjuvant chemotherapy), we wonder whether the trial results would have been the same as observed. In this light, one could surmise that this study demonstrates that combination ET is perhaps as efficacious as but not superior to adjuvant chemotherapy in this patient subset. The results of this trial, however, do provide encouraging support for the premise that combination ET is a reasonable therapeutic option for systemic adjuvant treatment in patients unable to undergo adjuvant chemotherapy for some reason. This may need confirmation in future trials.

Finally, it is interesting to note that among patients in this study receiving 5 years of treatment with tamoxifen, not a single hypercoagulable event was observed. This is in variance with several previous trial results, which have noted a mild elevation in the thrombotic-event risk in patients treated with tamoxifen for prolonged time periods.2,3 We therefore applaud the efforts of the study group in designing an important trial, but we question the authors’ conclusion of superiority of the combination ET.

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In Reply: I am offering this letter in response to the letter titled “Paradigm Shift in Adjuvant Treatment of Receptor-Positive Premenopausal Breast Cancer Patients? Not Yet!” from Drs M. Samur and H. S. Bozuk. In their letter, Drs Samur and Bozuk raise excellent points about the lessons that may be drawn from the trials of Jonat and Jakesz. Of course, in the time since Jonat and Jakesz studies were designed, it has been shown that several chemotherapy combinations are superior to cyclophosphamide, methotrexate, and fluorouracil (CMF), or to CMF equivalents, such as doxorubicin and cyclophosphamide (AC). These chemotherapy combinations include cyclophosphamide, epirubicin, and fluorour-
ractinomycin, AC, or paclitaxel, and perhaps dose-dense AC and paclitaxel or A, followed by T, followed by C. Of course, these treatments have not, as yet, been compared with hormonal therapy in conjunction with either ovarian ablation alone, or with ovarian ablation plus tamoxifen or an aromatase inhibitor.

One might nonetheless wish to make the paradigm shift to assume that for premenopausal-hormone–receptor women, it is hormone therapy that should be considered the core treatment with or without the addition of chemotherapy, rather than chemotherapy being the core treatment with or without the addition of hormone therapy.

In light of this, many women with hormone-receptor–positive breast cancer, at low to moderate risk of recurrence, may be best treated with endocrine therapy alone. Future studies should then examine the incremental benefit risk of chemotherapy added to the core of endocrine treatment.

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REFERENCES


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In Reply: Thank you for giving us the opportunity to respond to the letters relating to the Zoladex Early Breast Cancer Research Association (ZEBRA) trial comparing goserelin (Zoladex; AstraZeneca, Macclesfield, United Kingdom) with cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy in premenopausal patients with early breast cancer.

First, in response to the comments by Drs Samur and Bozcuk, the conclusion of the ZEBRA trial is that goserelin offers an effective alternative to CMF chemotherapy — these are the findings of the trial. From the evidence available to date, it is not absolutely clear that anthracycline-containing regimens demonstrate superiority over CMF in estrogen-receptor– (ER-) positive premenopausal patients; trials to assess the relative merits of different regimens in this patient population are needed.

With respect to the comments by Dr Malayeri, we agree with the author that during recent years, it has become recognized that overexpression of Her-2/neu B-2, we feel, is associated with poor prognosis and a possible decrease in expression, and this was equally distributed between the two treatment groups.

The ZEBRA trial was a large randomized study, and the treatment groups (goserelin 3.6 mg v CMF) were similar with respect to patient characteristics, primary tumor characteristics, and local therapy or radiotherapy. We therefore believe it unlikely that there would have been any relevant imbalance in neurelB-2 status between treatment groups in this study. Furthermore, for patients with ER-positive tumors (ie, 65% of patients disease-free at 5 years in both treatment groups), the results of the ZEBRA trial indicate that both goserelin and CMF are effective treatments in this patient population, with these results being consistent with previous findings for adjuvant therapies in premenopausal patients.2

In summary, although we agree that future studies should consider including analyses of predictive markers such as neurelB-2, we firmly believe that the results of the ZEBRA trial are robust and that goserelin is a valuable treatment option for premenopausal patients with ER-positive, node-positive disease.

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REFERENCES


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In Reply: The point of Drs Samur and Bozcuk is well taken and was often discussed during scientific meetings. The main problem is that chemotherapy was given for many years without knowledge of the steroid hormone receptors, because it was believed that in premenopausal patients, steroid hormone receptor status was not a predictive marker for adjuvant treatment.1 Therefore, little information is available about the benefit of anthracyline- and taxane-containing regimens, especially in direct comparison to endocrine treatment.

In a trial presented by Roche et al,2 complete endocrine blockade is superior to fluorouracil, doxorubicin, and cyclophosphamide (FAC) 50; however, this difference was not significant because of a low event-rate. Taking into account the importance of induction of amenorrhea in response to adjuvant chemotherapy, one has to consider the trial presented by Nabholz et al.3 Their results showed that amenorrhea was induced by FAC by about 55% and by docetaxel, doxorubicin, and cyclophosphamide by 55%, which is far lower than the rate of amenorrhea induced by cyclophosphamide, methotrexate, and fluorouracil (CMF), as presented in our article, as well as by Jonat et al.4,5 Therefore, it is not necessarily true that in premenopausal, receptor–positive patients, anthracyline- or taxane-containing regimens have to be superior to CMF, as shown in other patient cohorts. In order to clarify this statement and follow up on the issue of chemotherapy plus tamoxifen versus goserelin plus tamoxifen, we desperately need more well conducted clinical trials to be performed.

To answer the question of Dr Malayeri, we have analyzed Her-2/neu status in 568 patients in the Austrian Breast and Colorectal Cancer Study Group Trial 5.6 We found that 12.2% of patients experienced Her-2/neu overexpression, and this was equally distributed between the two treatment groups. What we found and presented at the San Antonio Breast Cancer Symposium in December, 2002,6 was that the overexpression of Her-2/neu was a significant indicator for poor prognosis, especially for overall survival.

Regardless whether the treatment is tamoxifen plus goserelin or CMF, patients with Her-2/neu overexpression have a significantly poorer outcome; however, this is a retrospective analysis of a large patient cohort. We believe that patients with overexpression of Her-2/neu are undertreated by either of these two therapy modalities.

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Correction to “Congestive Heart Failure After Treatment for Wilms’ Tumor”

To the Editor: The method for estimating the lung dose in our article, previously published in the April 1, 2001, issue of the Journal of Clinical Oncology,1 relied on addition of computerized dose data. The radiation oncologists on the National Wilms’ Tumor Study Group Study Committee pointed out that two of the dose estimates in Table 2 of the published manuscript appeared very high. As a result, all of the doses of those who developed congestive heart failure and the controls were reviewed. The result of this review was a correction of two of the 35 lung radiation dose estimates. These two changes resulted in minor changes in the relative risk estimates in the multiple regression analysis models in Tables 3 and 4 of the published manuscript.

The revised risk for girls was estimated to be approximately four times that for boys with the same level of cumulative doxorubicin exposure and of radiation to lung and left abdomen (P < 0.004). The revised risk was estimated to increase by a factor of 3.2 for each additional 100 mg/m² of doxorubicin among patients of the same sex who received the same level of cumulative radiation to the lungs and abdomen (P < 0.001). The revised risk

Table 2. Characteristics of 35 Patients Who Developed Congestive Heart Failure

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NOTE: Data in bold have been adjusted from original data in Green et al.1
Abbreviations: WT, Wilms Tumor; CHF, congestive heart failure.

*Recorded dose is the total resulting from overlapping fields and “boost” doses given over time in two or more radiation therapy courses after relapse(s).
of congestive heart failure was estimated to increase by a factor of 1.6 for every 10 Gy of lung irradiation, and by 1.8 for every 10 Gy of left abdominal irradiation. By contrast, there was no evidence that right abdominal radiation increased the risk ($P = .77$).

The revised results for the categorical variable analysis demonstrated a clear trend of increasing risk with increasing doses of doxorubicin above 300 mg/m$^2$ and with increasing lung radiation. Patients who received left or whole abdomen radiation had a higher risk of congestive heart failure than did patients who received either no radiation therapy or radiation therapy only to the right abdomen (related risk, 3.5; $P = .02$).

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