Endocrine Therapy for Breast Cancer

Review Article [1] | April 01, 2000
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In an admirably concise fashion, Dr. Pritchard summarizes the results of trials randomizing tens of thousands of women in order to evaluate various types and uses of endocrine treatment over more than 50 years. I would never have predicted these results when I began my medical career in the early 1970s, or even as late as 1984 when the first overviews of breast cancer therapy were performed by Richard Peto and his colleagues at Oxford. However, some conclusions from these studies are now inescapable. Whether the patient is premenopausal or postmenopausal, and whether she has early- or advanced-stage breast cancer, the treatment of choice if the tumor is estrogen receptor positive is some form of endocrine manipulation.

The Unanswered Question

The question that must be addressed now is, what should we do with chemotherapy in these patient groups? Between 1970 and 1990, we asked: Does the addition of endocrine treatment to chemotherapy improve the disease-free and overall survival of patients with estrogen receptor–positive tumors? If so, how much additional benefit is imparted by adding endocrine therapy? The answers to these questions are found in Dr. Pritchard’s review: “yes” and “a lot.”

Now, we must turn this around and ask whether chemotherapy provides similar additive benefits to endocrine treatment. Dr. Pritchard touches lightly on this subject in her article.

The use of chemotherapy in combination with endocrine treatments is particularly important in light of increasing evidence that adjuvant chemotherapy is less effective in patients with receptor-positive tumors.[1] On average, the reduction in the odds of recurrence or death from adjuvant chemotherapy is 33% to 50% less among women with receptor-positive tumors compared to those with receptor-negative tumors. This is true for younger and older women, but, in the Oxford overview, the differences reached statistical significance in only one of the four comparisons. The concomitant use of tamoxifen (Nolvadex) in most of these patients confounds this evaluation. Thus, at present, we cannot determine precisely whether chemotherapy is less effective in estrogen receptor–positive patients, or whether it adds less benefit in patients who are receiving concomitant tamoxifen.

In the metastatic disease setting, the addition of chemotherapy increases response rate and, to a lesser extent, time to disease progression but has little effect on overall survival.[2] Since chemotherapy adds considerable toxicity, it is doubtful that chemohormonal combinations will result in a net improvement in quality of life. Unless the patient has a low estrogen receptor value and evidence of aggressive disease (eg, a short disease-free interval and liver metastases), the use of endocrine treatment alone seems the best way to manage the patient immediately after first recurrence.

Adjuvant Tamoxifen vs Tamoxifen Plus Chemotherapy

Most of the studies in the adjuvant setting have been limited to a comparison of tamoxifen alone with tamoxifen plus chemotherapy in postmenopausal patients. Only a handful of very small trials have compared ovarian ablation with ovarian ablation plus chemotherapy in premenopausal women. In fact, the number is too small for these studies to have been included as a subset analysis in the Oxford overviews.

In the most recent overview, the comparison of tamoxifen alone with tamoxifen plus chemotherapy included only 640 patients under age 50 years. The reduction in the annual odds of death was 21% ± 13%, which is not statistically significant.[1] Based on this small sample, therefore, it would be inappropriate to conclude that chemotherapy is additive or synergistic with tamoxifen in this younger age group.

In contrast to the younger women, almost 9,200 women ≥ 50 years old have been enrolled in
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studies comparing tamoxifen alone with tamoxifen plus chemotherapy.[1] In the Oxford overview, the reduction in the annual odds of death from adding chemotherapy was 19% ± 3%. Two important confounding factors must be taken into consideration when evaluating these data, however. First, most of these patients received a suboptimal duration of tamoxifen therapy. Although the trials that contributed to this estimate are not listed in the most recent publication of the Oxford overview, we know from prior overviews that more than 3,000 of the patients were treated with tamoxifen for 1 year or less and more than 1,400 received treatment for 2 years. Second, between 10% and 20% of patients ≥ 50 years of age are still premenopausal. The addition of chemotherapy likely has a different effect in premenopausal and postmenopausal women.

**Studie Evaluating 5 Years of Tamoxifen Therapy**

At least two studies treated patients with adjuvant tamoxifen for 5 years; together, these studies account for 1,736 of the patients in this overview analysis. In one of these trials, the Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group (GROCTA) study from Italy, 510 premenopausal and postmenopausal patients were randomized to tamoxifen for 5 years or tamoxifen for 4 years following 1 year of adjuvant chemotherapy.[3,4] The chemotherapy consisted of six cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF) followed by four cycles of epirubicin (Ellence). Patients treated with tamoxifen alone fared better than those treated with chemotherapy and did as well as those treated with the combination of tamoxifen plus chemotherapy. The authors concluded that tamoxifen alone is the treatment of choice for postmenopausal women, but they were less certain that this was true of younger women, especially those with very aggressive tumors.

In the second study, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-16 trial, 1,245 women ≥ 50 years old were randomized to tamoxifen alone for 5 years or tamoxifen plus chemotherapy.[5] For most of the women, chemotherapy consisted of four cycles of Adriamycin (doxorubicin) plus cyclophosphamide (AC). However, 75 of the patients were treated with melphalan (Alkeran) plus fluorouracil and 343 received melphalan, doxorubicin, and fluorouracil. The percentage of patients in this study who were premenopausal has not been reported. However, 43% were between the ages of 50 and 59 years, and it is reasonable to assume that about 20% of these patients were premenopausal. Patients treated with both tamoxifen and chemotherapy had a significantly better disease-free and overall survival compared to those treated only with tamoxifen. This was not reported separately for the different age groups, but there was evidence of benefit in those with tumors that were marginally positive, as well as those with strongly positive estrogen receptor values.

**Current Conclusions**

When all of these data are considered together, the following conclusions can be made about the combination of endocrine therapy and chemotherapy in patients with estrogen receptor positive tumors:

1. In the metastatic disease setting, individual studies have not demonstrated a survival benefit from the combination of endocrine therapy and chemotherapy in patients with estrogen receptor[†]positive tumors. Moreover, such combinations are likely to be associated with a poorer quality of life than endocrine therapy alone.

2. In the adjuvant setting, data comparing endocrine therapy alone vs endocrine therapy plus chemotherapy in premenopausal women are inadequate to draw meaningful conclusions.

3. Among postmenopausal women, most of the studies have used a suboptimal duration of tamoxifen treatment.

4. Most of the compelling evidence suggesting that tamoxifen plus chemotherapy is superior to chemotherapy alone comes from the NSABP B-16 trial. Although NSABP B-16 is a large, well-designed trial, its results conflict with those of the GROCTA trial, which is smaller but still quite substantial.

**Recent ECOG/Intergroup Data**

At the 1999 American Society of Clinical Oncology (ASCO) meeting, the Eastern Cooperative Oncology Group (ECOG) and intergroup presented data from a trial in which premenopausal women with estrogen receptor[†]positive tumors were randomized to receive CAF alone, CAF plus goserelin
(Zoladex), or CAF plus goserelin and tamoxifen for 5 years.\[6\] Estrogen levels measured at the completion of chemotherapy were used to define patients as physiologically premenopausal or postmenopausal at the time that they began endocrine treatment. Only patients whose post-chemotherapy estrogen levels were in the premenopausal range benefited from the addition of goserelin, and only those with post-chemotherapy estrogen levels in the postmenopausal range derived a benefit from the addition of tamoxifen.

These observations indicate the importance of performing separate analyses of comparisons of endocrine therapy alone vs endocrine therapy plus chemotherapy in premenopausal and postmenopausal women. Optimal endocrine therapy in this younger group must include ovarian ablation and tamoxifen. A study that compares tamoxifen alone with tamoxifen and chemotherapy in premenopausal women (such as NSABP B-16) may really be comparing inadequate endocrine therapy (tamoxifen) with optimal endocrine therapy (chemically induced ovarian ablation plus tamoxifen for 5 years).

References:


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