The Early Breast Cancer Trialists Collaborative Group (EBCTCG) Process: Is it Still Relevant in 2006?

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The Early Breast Cancer Trialists Collaborative Group (EBCTCG) overview process held its first meeting in 1984. At that time, the Secretariat led by Mr. Richard Peto at Oxford University, contacted as many Clinical Trialists as possible who were carrying out randomized controlled clinical trials of any type of adjuvant therapy for breast cancer, and obtained their collaboration in sending individual patient data from these trials for an overview or meta-analysis. The Trialists and the Oxford Secretariat met for the first time in 1984 at Heathrow Airport. Trialists presented brief summaries of their studies and their results and the Oxford Group followed with the meta-analyses. Both the process and its results were new and exciting. At that time, many North Americans had believed that adjuvant chemotherapy was effective, and many Europeans, that adjuvant tamoxifen was effective, but the overview process clearly showed that each reduced recurrence, and increased overall survival. Even those who were initially skeptical were won over to the process, and five yearly meetings were held in 1990, 1995, 2000, and 2005.

The overview methodology comprises examination of outcomes which include first recurrence (e.g., local recurrence, distant recurrence, second primary cancer, death, and contralateral breast cancer), as well as both breast cancer specific and overall death rates. The data is checked for internal consistency and amended and updated by correspondence. It is important to realize that the methodology involves analyzing each trial separately, creating one log rank statistic per trial, and allows stratification by age, nodal status, receptor status, and other criteria. The log rank statistics can then be combined to give an overall estimate of the effect of different treatments. Women in one trial are compared directly only with the women in the same trial. A weighted average of the effect in each separate trial is obtained and then the overview process provides an overall estimate of the direction and magnitude of the effects of treatment in all trials. The process does

not assume that the effect of treatment is the same in each trial.

In 1984, as mentioned above, the exciting results included verification of the effects of tamoxifen and of chemotherapy. In addition, many small underpowered trials of ovarian ablation by surgery or radiation were combined to demonstrate an overall benefit on recurrence-free survival and overall survival in premenopausal women.

In 1990, data from the Overview suggested that longer tamoxifen treatment appeared superior to shorter, and that tamoxifen effects were definitely much greater and perhaps restricted almost completely to women with estrogen receptor (ER) positive disease. It was also demonstrated at this time that tamoxifen reduced the rate of contralateral breast cancer, and that chemotherapy was effective in both younger and older women.

By 1995, the Overview demonstrated a huge magnitude of effect of 5 years of tamoxifen, and showed that 5 years of tamoxifen was clearly better than 1 or 2. It also became apparent that tamoxifen prevented contralateral breast cancer only in women with ER positive disease, and that anthracycline-containing regimens in general were better than CMF (cyclophosphamide, methotrexate and fluorouracil).

In 2000, the Overview had 15-year follow-up on many treatment comparisons. This length of follow-up proved particularly interesting since it demonstrated that the effects of chemotherapy were sustained at 15 years of follow-up in both older and younger women. It was also found that the effect of chemotherapy appeared greater in ER negative than in ER positive women. Furthermore, the effects of 5 years of tamoxifen were sustained and of great magnitude at 15 years of follow-up. In addition, as a result of data from newer trials examining the role of five years of tamoxifen vs longer treatment with tamoxifen, the window was opened to the question of whether tamoxifen for longer than five years might actually be

of greater benefit than 5 years of tamoxifen, a question which had earlier been considered settled by some, following results from the NSABP [1] and Scottish trials [2, 3]. Ovarian suppression or ablation was found to be of continuing efficacy at 15 years of follow-up, but was not significantly so when added to chemotherapy.

The strength of the Overview process includes the fact that has, up until now, included over 90% of all worldwide data on most of the questions under analysis (91% re chemo and 92% re tamoxifen in 2000). Data is checked and cross checked, and continued efforts to access >90% of the data will add to the comprehensive nature of this process. The meta-analysis technique itself is extremely powerful. Also, however, the collaboration of the various investigators has led to an amazing amount of productive interaction and research planning amongst the various Clinical Trialists as well as between the Trialists and the Oxford Secretariat.

Moving into the 2005 Oxford Overview there was considerable frustration around timelines for publication of the 2000 data. A very important and comprehensive publication of this material did occur in early 2005 [4] however, and a further important publication from meta-analysis of locoregional therapy, particularly radiation therapy, was published in December of 2005 [5]. This paper was of great interest because it showed that effective radiation therapy which prevented locoregional recurrences was also associated with a significant overall survival benefit. This survival benefit was sustained, but was reduced to some extent by increased cardiovascular deaths occurring between 10 and 20 years of follow-up. Whether modern radiation techniques will prove less cardiotoxic will be seen by further follow-up and collaboration through the ongoing EBCTCG.

Other difficulties with the Overview process include philosophical differences concerning the role of subset analyses, a lack of detailed information on various biologic predictive factors such as progesterone receptor (PgR) and HER-2/neu status for many of the patients involved in the Overview, as well as lack of exact details about chemotherapy administration and compliance to oral therapies.

Nonetheless, the Overview will continue to have considerable power to examine many important questions which include the role of more than 5 years of tamoxifen vs 5 years of tamoxifen, the role of taxane vs non-taxane containing regimens, the role of bone marrow/stem cell transplant therapy vs conventional therapy, the role of ovarian suppression, the role

of the aromatase inhibitors (AIs), and the role of locoregional radiation therapy in improving locoregional recurrence, overall survival, breast cancer related survival, and cardiovascular related survival. The Overview also has great potential power for the examination of predictive factors and biologic markers if these can be more fully collected.

An update of the 2005 Oxford meeting will be held from September 11–13, 2006. Large amounts of additional data have been coming into the Secretariat in preparation for this meeting. Comprehensive updated information about trials of the taxanes, the AIs, bone marrow/stem cell transplant and a number of other topics will be available for meta-analysis and discussion. By June 23, 2006, data had arrived and had been processed upon newer updated data from 62 groups, comprising 81 new trials and 233 trials that had been updated. There were at that time, data on 64,000 randomized women in new trials, and updated data on 178,000 women in trials that had been updated. As the summer has progressed, additional data have been flowing in.

In spite of the increased size and power of individual trials and their ability to examine biologic markers, combining data from these large trials and including biologic markers in the meta-analysis process will continue to add additional benefit to what we can learn from individual trial data. In addition, long-term follow-up from individual trials examined by the meta-analysis process has provided extremely valuable and important information concerning the long-term results of our treatments for breast cancer. We believe that all Trialists should continue to support the EBCTCG process, which will remain very valuable for the foreseeable future.

References

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