EDITORIAL

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Preoperative Chemotherapy: Where Do We Go from Here?

Over the past two decades, we have witnessed dramatic advances in the treatment of breast cancer. Randomized prospective trials have shown that women with tumors 4 cm or larger can be treated with breast conservation in contrast to ablative surgical procedures.[1,2] The effectiveness of postoperative adjuvant systemic chemotherapy in prolonging overall survival was recently reviewed as a worldwide collaboration involving 133 randomized trials.[3] A multimodality treatment approach has been used for patients with locally advanced breast cancer (Stage IIIA–IIIB); this approach consists of neoadjuvant chemotherapy.[4,5] Soon thereafter, this neoadjuvant approach was applied to smaller, more operable breast cancers.[6] In fact, some authors have advocated minimizing or avoiding surgery completely by using this approach.[7] In this issue of the *Annals of Surgery,* Veronesi et al.,[8] one of the leading groups in breast cancer trials, reported a retrospective analysis of 227 patients with breast cancers 3 cm or larger who were given primary neoadjuvant chemotherapy. Tumor regression was observed in almost 90% of the patients, thus conservative surgery was possible and mastectomy avoided. The patients were treated with five different regimens of chemotherapy, although there appeared to be no significant differences among the various regimens.

The study by Veronesi et al. as well as other recent reports[9,10] raise an important issue regarding the selection of appropriate patients for this type of clinical trial. Two of the primary goals of preoperative chemotherapy are to avoid mastectomy and decrease the incidence of ipsilateral tumor recurrence. Although Veronesi et al. documented a local recurrence rate of 5.9% with breast conservation, similar local recurrence rates have been obtained without the benefit of preoperative chemotherapy.[11] Although each of the studies referenced have shown a dramatic decrease in the need for mastectomy, one should remember that preoperative chemotherapy may not be necessary on the basis of tumor size *per se.* For example, in the study by Veronesi et al., most of the patients had tumors 5 cm or smaller. This size would meet the accepted criteria for inclusion of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials and of our own institution's trials. Without preoperative chemotherapy, local recurrence rates of tumors without an extensive intraductal component are virtually identical to the local recurrence rate achieved by Veronesi et al.[11] Thus, depending on the criteria used for inclusion in a breast conservation approach, surgeon bias, and surgical techniques, patient selection may vary widely. Although the inclusion criteria may vary with the study and the investigator, Veronesi et al. demonstrated that tumors can be dramatically down-staged with preoperative chemotherapy, thereby minimizing the need for ablative surgery. The question remains, however, as to whether neoadjuvant chemotherapy reduces ipsilateral breast tumor recurrence and prolongs survival.

A third aim of preoperative chemotherapy is to assess its effect on overall survival, which cannot be assessed adequately in a retrospective analysis, but only in a prospective randomized trial. Recently, Powles et al.[12] randomized patients to neoadjuvant treatment consisting of four cycles of chemotherapy over 3 months before surgery, followed by another four cycles after surgery. These patients were compared with patients randomized to adjuvant therapy who received eight cycles of chemotherapy over 6 months after undergoing a definitive surgical procedure. Unfortunately, the study by Powles et al. may be too small to provide statistical significance on overall survival. More accurate results may be achieved from a much larger trial, such as the NSABP B-18 clinical trial, which evaluates preoperative chemotherapy in Stage I and II breast cancers. B-18 has accrued more than 1300 patients and with adequate follow-up should be able to assess the effect on overall survival as well as on ipsilateral tumor recurrence.[13]

Another important issue regarding the evaluation of preoperative chemotherapy is whether a correlation exists between response of the primary tumor to some biologic marker and to patient disease-free and overall survival. The current study by Veronesi et al. demonstrated

limited changes in the percentage of prechemotherapy and postchemotherapy estrogen receptor status. In an earlier report of a small cohort of patients included in this study, Bonadonna et al.[14] showed that tumor response was unrelated to age, menopausal status, ploidy, or thymidine-labeling index. Future trials on preoperative chemotherapy are needed to evaluate these as well as the newer biologic markers, such as angiogenesis, HER-2/*neu*, p53, and other tumor oncogenes. The establishment of a correlation between these biologic markers and outcome might then permit a predictable test of response to neoadjuvant chemotherapy. An accurate predictor of outcome could avoid the necessity of long-term follow-up currently required with the NSABP B-18 trial. Our recent report of a breast tumor antigen derived from the HER-2/*neu* oncogene might also serve as a biologic marker that may predict response to chemotherapy and/or responsiveness to future therapies using biologics; additionally, this antigen may provide a method for stimulating an endogenous immune response in the patient.[15]

The final goal of neoadjuvant therapy is to answer the question concerning the comparison of preoperative chemotherapy and postoperative adjuvant chemotherapy. The current study suggested that the combination of fluorouracil, epirubicin, and cyclophosphamide was particularly effective in reducing tumor size; however, there was no statistical difference between the various chemotherapy regimens and shrinkage of the primary tumor or recurrence rates. Future trials will not only compare various regimens of chemotherapy, but also, more importantly, determine whether a preoperative regimen is more effective than no adjuvant treatment and whether preoperative chemotherapy is as or more effective than the same regimen given in an adjuvant setting. In the above-mentioned study by Powles et al.,[12] the study design compared postoperative chemotherapy with a combination of preoperative and postoperative chemotherapy, thereby making it impossible to define the importance of preoperative chemotherapy alone; it is hoped that the NSABP B18 trial will answer this question.

In the current study, Veronesi et al. also addressed some very important technical issues. Evaluation of the tumor by frequent physical examination and strict mammographic follow-up is very important. It is also important to use a permanent mark (tattooing) to identify the original tumor size once neoadjuvant therapy is complete. Accurate assessment and inclusion of microcalcifications in the excised specimen using intraoperative specimen radiographs as well as liberal use of margin assessment cannot be overemphasized. Because more breast conservation is performed, techniques for reconstruction of the remainder of the breast tissue have become very important in obtaining an optimal cosmetic outcome.

In summary, Veronesi and colleagues have provided us with a provocative study that conclusively shows a significant downstaging of primary tumor size after preoperative chemotherapy. There is temptation to begin using this strategy for all patients in more frequent attempts to avoid radical surgery; however, a wonderful opportunity to study the biologic and clinical correlates to this treatment would be lost. Identification of the effects of preoperative chemotherapy on various biologic parameters and growth factors will assist in the design of future clinical trials. In addition, perhaps such identification will provide predictors that would shorten the necessary length of follow-up. Neoadjuvant chemotherapy also provides an excellent model with which to compare different chemotherapy regimens and to identify the most effective preoperative chemotherapy regimen. It further allows for comparison with proven adjuvant regimens of systemic treatment. Once again, we find ourselves indebted to Veronesi and his colleagues for defining a biologic question and finding a possible clinical solution. Similarly, Fisher and Wolmark[13] as well as the NSABP investigators will help to define many of the parameters regarding preoperative chemotherapy through the NSABP B-18 trial. The challenge to other surgical investigators will then be to obtain vital information concerning the biologic and clinical interrelationships observed after preoperative chemotherapy. Judicious optimization and careful evaluation of randomized trials will ultimately serve our patients well.

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