A Multidisciplinary Approach to the Management of Breast Cancer, Part 2: Therapeutic Considerations

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New approaches to breast cancer treatment have enhanced clinical outcomes and patient care. These approaches include advances in breast irradiation and hormonal and systemic adjuvant therapies. In addition to the identification of new drug targets and targeted therapeutics (eg, trastuzumab), there is renewed reemphasis in the development of biomarkers for the prediction of response to therapy. One example is the pharmacogenetics of tamoxifen metabolism and the individualization of hormonal therapy. The current treatment of breast cancer continues to evolve rapidly, with new scientific and clinical achievements constantly changing the standard of care and leading to substantial reductions in breast cancer mortality. The goal of this article is to provide clinicians who care for women with breast cancer a multidisciplinary, state-of-the-art approach to the treatment of these patients.

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Part 1 of this contribution discussed the multidisciplinary approach needed for the prevention and diagnosis of breast cancer. This team of experts includes medical oncologists, breast radiologists, breast pathologists, surgical breast specialists, radiation oncologists, geneticists, and primary care physicians.1 The current contribution provides clinicians who care for women with breast cancer a multidisciplinary, state-of-the-art approach to the treatment of these patients.

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WHOLE BREAST IRRADIATION VS PARTIAL BREAST IRRADIATION: WHAT IS NEW?

Breast-conserving surgery (lumpectomy) is considered standard treatment of early-stage breast cancer. Randomized trials have shown that breast irradiation after such surgery reduces the risk of recurrence in the breast and thus improves the likelihood of breast preservation.2 To date, no subset of patients has been identified in whom radiation can be eliminated when local control and breast preservation are end points.3 Typically, the radiation schedule used in the United States has been 45 to 50 Gy in 5 to 5 1/2 weeks to the entire breast sometimes followed by a tumor bed boost of an additional 10 to 15 Gy in 1 to 1 1/2 weeks. Local recurrence after such an approach ranges from 6% to 14%, and survival is equivalent to the results of patients undergoing mastectomy.2,4

However, some women who are candidates for a breast-conserving approach choose mastectomy instead because of issues related to the inconvenience of such a protracted treatment regimen.5 In the United States, only 43% of patients with stage I and II disease undergo breast-conserving surgery, and of these, 14% do not receive postoperative radiotherapy.6 To address this issue of inconvenience, many investigators have explored the use of shorter treatment schedules. Whelan et al7 reported a Canadian randomized trial that compared 42.5 Gy in 16 fractions to 50 Gy in 25 fractions. A total of 1234 women with lymph node–negative invasive breast cancer were entered into this study. With a median follow-up of 69 months, no difference in local recurrence-free survival or overall survival rates was detected between the study arms. The percentage of patients with excellent or good global cosmetic outcome at 3 and 5 years was also comparable, thus suggesting that the more convenient shorter schedule is an acceptable alternative to the standard 5-week regimen. This Canadian hypofractionated regimen has not been widely adopted in the United States but is used for some patients.

Traditionally, standard radiation after lumpectomy has targeted the entire breast to treat clinically occult disease.8 More recently, techniques for partial breast irradiation (PBI), which limits the radiation to the lumpectomy surgical bed, have been introduced. These techniques are based
on the assumption that in selected patients it may not be necessary to irradiate the entire breast. This approach is supported by the finding that most breast recurrences after breast conservation treatment with lumpectomy and whole breast irradiation occur in or near the tumor bed. Partial breast irradiation offers the potential advantage of reduced treatment-related toxic effects by limiting the volume of normal tissue such as heart and lung that is irradiated. In addition, PBI has the potential to significantly shorten the treatment time since accelerating treatment is possible when treating a more limited tissue volume. The most common PBI treatment regimen delivers 34 Gy in 10 fractions given twice daily for 5 days to a volume that includes the lumpectomy cavity with a margin of 1 to 2 cm. Most data from a number of single-institution studies that use PBI suggest promising local control and cosmesis in carefully selected and properly treated patients.\textsuperscript{10,12} In a matched-pair analysis, Vicini et al\textsuperscript{10} demonstrated the equivalence of PBI to whole breast irradiation. Local recurrence, failure in the breast beyond the tumor bed region, cosmesis, and survival were identical for the 2 treatment approaches, with a median follow-up of 5 years.

In the United States, PBI initially was delivered with interstitial brachytherapy at a low dose rate, but more recently this has been changed to a high dose rate. High rates of local control and good cosmetic results have been reported.\textsuperscript{13} However, interstitial brachytherapy is a relatively complex procedure that requires considerable technical expertise. Thus, other methods of PBI have been introduced. One such method is an inflatable balloon-based interstitial catheter (MammoSite, Proxima Therapeutics, Alpharetta, GA) that was approved by the Food and Drug Administration (FDA) in 2002 and is now the most widely used form of PBI worldwide.\textsuperscript{14} However, in some cases the lumpectomy cavity size, shape, or location limits use of this device. More recently, the use of a noninvasive technique, 3-dimensional conformal external beam irradiation, has been explored. Early reports suggest promising results.\textsuperscript{15,16} The Radiation Therapy Oncology Group conducted a phase 1/2 trial (0319) to evaluate the use of this technique.\textsuperscript{17} Patients received 38.5 Gy in 3.85-Gy fractions delivered twice daily. In this preliminary analysis of the first 42 evaluable patients, accelerated PBI was shown to be technically feasible and reproducible in a multi-institutional trial. Single-fraction, large-dose intraoperative radiation with either photons or electrons at the time of the lumpectomy is being evaluated in 2 clinical trials in Europe.\textsuperscript{18,19} Regardless of the exact method, the key to effective PBI is the use of highly reproducible techniques with excellent quality assurance.\textsuperscript{20} In addition, careful patient selection is mandatory. To that end, the American Brachytherapy Society\textsuperscript{21} and the American Society of Breast Surgeons\textsuperscript{22} have published similar guidelines for PBI. The American Brachytherapy Society suggests the use of PBI in patients older than 45 years with unifocal, invasive ductal carcinoma that measures less than 3 cm with negative microscopic surgical margins and negative lymph nodes. Both societies recommend enrollment in clinical trials if possible and appropriate informed consent.

The long-term efficacy of PBI compared with whole breast irradiation needs to be confirmed in prospective, randomized trials. The National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Radiation Therapy Oncology Group are currently conducting such a phase 3 randomized clinical trial (B39/R0413). This trial will randomize 3000 patients after lumpectomy for early-stage breast cancer to either whole breast irradiation or PBI. The trial will allow use of any of 3 PBI techniques: interstitial brachytherapy, inflatable balloon-based interstitial catheter, or 3-dimensional conformal external beam irradiation. Thus, this trial will help to identify the most optimal means of delivering PBI and the patient population most suitable for its use. If proved effective, PBI may allow more women to choose breast conservation therapy.

**ADJUVANT CHEMOTHERAPY**

Adjuvant systemic chemotherapy plays an important role in the management of patients with resected breast cancer, especially when the risk of recurrence despite local therapy is estimated to be greater than 10% at 10 years.\textsuperscript{23} Clinical trials performed during the past 20 years that involve thousands of women have shown that adjuvant chemotherapy significantly reduces the risk of recurrence and prolongs overall survival.\textsuperscript{24,25} The agents commonly used in the adjuvant setting include anthracyclines, alkylating agents, taxanes, and antimetabolites. Schedules of these agents include weekly and every 2- or 3-week regimens administered during periods that extend from 2 months up to 6 months (duration of treatment varies by tumor stage). Historically, the use of more intense or longer duration chemotherapy scheduling has been based on tumor stage. For example, women with early-stage breast cancer have traditionally been treated with 4 cycles of anthracycline-based chemotherapy (eg, 4 cycles of combination doxorubicin and cyclophosphamide). In contrast, patients with more advanced-stage breast cancer (eg, stage II or III) have been considered for additional therapies (eg, taxanes) in which the total duration may last 4 to 6 months. Some of the commonly used regimens include 4 cycles of doxorubicin-cyclophosphamide followed by 4 cycles of paclitaxel; the combination docetaxel, doxorubicin, and cyclophosphamide; the combi-
nation fluorouracil, doxorubicin, and cyclophosphamide; or the combination cyclophosphamide, methotrexate, and fluorouracil. If radiation therapy is indicated, it is routinely administered after completion of chemotherapy. In general, systemic chemotherapy decreases the risk of recurrence by approximately 30% to 50%, with greater absolute benefit in estrogen receptor–poor or absent breast cancer.26

Because many patients do not benefit from chemotherapy, current research is focused on identifying the biological subsets of patients who benefit from adjuvant chemotherapy. Current approaches to the decision making include integration of classic prognostic factors that should always be considered, including age, performance status, and end-organ function (liver, renal, and cardiac). In terms of molecular markers in tumors, this is an evolving area of research that affects the selection of targeted agents, such as selective estrogen receptor modulators and trastuzumab. Current trials are also evaluating gene profiles in tumor tissue to determine the potential likelihood of benefit from various chemotherapeutic agents.

ADJUVANT ENDOCRINE THERAPY

Appreciation has increased in the substantial value of adjuvant endocrine therapy for women with early-stage breast cancer whose tumors express the estrogen and/or progesterone receptor. Until recently, tamoxifen had been the standard of therapy in the adjuvant setting for postmenopausal women with early-stage breast cancer since its approval by the FDA in 1986 for node-positive disease and in 1990 for node-negative disease. For premenopausal women, tamoxifen remains the only endocrine agent approved by the FDA and remains an integral component of optimal therapy. The duration of tamoxifen therapy is currently considered to be no longer than 5 years, primarily based on a single large clinical trial that found 10 years of tamoxifen use to be inferior to 5 years.23 The Early Breast Cancer Trialists’ Collaborative Group (Oxford Overview), which considered all randomized trials, found that approximately 5 years of tamoxifen use reduced the annual breast cancer death rate by 31%.26

A substantial amount of endocrine therapy research has been conducted in postmenopausal women during the past decade. Initially, in the advanced disease setting, a substantial body of evidence demonstrated the value of aromatase inhibitors (AIs),21 and this stimulated multiple trials of the AIs vs tamoxifen in early-stage disease. Substantial data have been generated that provide evidence for their use in the management of postmenopausal patients in standard clinical practice. Three different AIs (anastrozole, exemestane, and letrozole) have been evaluated in 3 different settings: (1) initial therapy vs tamoxifen, (2) a switching strategy after 2 to 3 years of tamoxifen, and (3) extended adjuvant therapy after 5 years of tamoxifen.

In the initial therapy setting, 2 major trials have randomized women to either tamoxifen or an AI for 5 years. Both the Arimidex, Tamoxifen, Alone or in Combination trial,28 which examined anastrozole, and the Breast International Group trial,29 which examined letrozole, showed an improvement in disease-free survival (DFS), but to date no improvement has been seen in overall survival. The reduction in DFS events was 17% to 18% in both trials, with the absolute reduction at 5 years being 2.8% to 2.9%. Both trials showed a difference in toxicity profile between tamoxifen and the AI, with tamoxifen being associated with more thromboembolic and gynecologic events. The AIs were also associated with more fractures and arthralgias. Clearly, attention must be paid to bone health, specifically bone mineral density, in women who receive AIs.30

In patients who have already received approximately 2 years of tamoxifen therapy, 3 trials have examined the value of switching to an AI vs continuing tamoxifen therapy for the full 5 years.31-33 The largest of these trials,31 the Intergroup Exemestane Study, has shown a significant improvement in DFS and, when estrogen receptor–negative patients who would not be expected to benefit were excluded, the survival advantage was statistically significant (P=.05). Again, the toxicity patterns were similar to those aforementioned, with more fractures and fewer thromboembolic events in patients who switched to the AI.

Women who have received 5 years of tamoxifen should be considered in terms of residual risk of recurrence of the breast cancer. Ravdin and Davis34 used the Oxford Overview data to estimate residual risk of relapse in patients who completed 5 years of tamoxifen therapy, and they found that the average annual risk of relapse from years 6 through 10 was 2.0% for patients with node-negative disease and 4.4% for women with node-positive disease. Two trials have evaluated the use of AIs in such patients vs no further treatment.35,36 The larger of these trials is the National Cancer Institute of Canada Clinical Trials Group MA.17.35 This trial showed a significant advantage for letrozole in DFS for all patients regardless of whether they had lymph node metastasis and a survival advantage that was statistically significant for patients with node-positive disease. The second trial, from the Austrian Breast and Colorectal Cancer Study Group,36 found a similar advantage for anastrozole in improving DFS.

On the basis of the evidence presented, AIs are clearly a positive addition to the clinician’s armamentarium for adjuvant therapy for postmenopausal women with early-stage breast cancer. Direct cross-setting comparisons of the findings in the initial treatment setting and switching setting as aforementioned are confounded by the fact that the popula-
THERAPEUTIC CONSIDERATIONS OF BREAST CANCER

Adjuvant Endocrine Therapy and Ductal Carcinoma In Situ

The use of adjuvant hormonal therapy, specifically tamoxifen, is becoming more standard in the clinical management of patients with ductal carcinoma in situ (DCIS) in the setting of radiotherapy. The NSABP B-24 trial randomized 1804 women with DCIS to receive tamoxifen or placebo after excision and radiotherapy. An overall benefit was seen in the prevention of breast cancer events in patients with estrogen receptor–positive tumors who received tamoxifen. Similarly, the United Kingdom/Australia and New Zealand DCIS trial found that tamoxifen decreased the overall rate of recurrence of DCIS but did not reduce the incidence of invasive cancer. Currently, it is unclear whether tamoxifen has any value in the setting of patients diagnosed as having DCIS who undergo wide excision alone, but this remains to be defined. In addition, clinical trials are currently testing newer drugs (AIs) that may have the potential to further reduce local recurrence.

Adjuvant Endocrine Therapy and Metastatic Disease

Endocrine therapy is the treatment of choice for women with estrogen receptor– and/or progesterone receptor–positive breast cancer, except when clinical reasons exist to move directly to chemotherapy, such as a rapid tempo of disease progression or the presence of a visceral crisis, such as lymphangitic pulmonary metastasis. For postmenopausal women, numerous endocrine agents are available, including the selective estrogen receptor modulator tamoxifen; the third-generation AIs (anastrozole, exemestane, and letrozole); the estrogen receptor down-regulator fulvestrant; the progestins (megestrol acetate and medroxyprogesterone acetate); and the androgen fluoxymesterone; and the estrogens. In premenopausal women, data are available for tamoxifen and the luteinizing hormone-releasing hormone (LHRH) analogues both alone and in combination and an AI in combination with an LHRH analogue. Endocrine therapies are generally administered sequentially until endocrine resistance is established or clinical reasons exist to proceed to cytotoxic chemotherapy, with the challenge being the most appropriate sequence of endocrine therapy administration.

For postmenopausal women, the introduction of the AIs as an alternative to tamoxifen or after tamoxifen for adjuvant therapy for those with resected hormone receptor–positive breast cancer has added a level of complexity to determining which endocrine agent to use in the metastatic disease setting. Several categories of patients can be identified that will guide treatment selection: (1) tamoxifen-sensitive (no prior AI), (2) tamoxifen resistant (no prior AI), and (3) AI resistant (with or without prior tamoxifen). Well-conducted phase 3 trials provide evidence for choosing first-line therapy for advanced disease in categories 1 and 2. For tamoxifen-sensitive patients, defined as no prior tamoxifen or at least 1 year of not taking adjuvant tamoxifen before disease recurrence, one can choose either nonsteroidal AI anastrozole or letrozole. For tamoxifen-resistant patients, the choices are the nonsteroidal AIs, the steroidal AI exemestane, or the estrogen receptor down-regulator fulvestrant. Fewer data are available in category 3 (AI resistant) on which to base the choice of endocrine therapy. There are no published phase 3 (comparative) trials of agents in patients who have experienced disease progression while taking an AI. Efficacy data are available for exemestane, fulvestrant, and high-dose estrogens, and retrospective data are available for tamoxifen. For the patient resistant to a nonsteroidal AI, one can choose either exemestane or fulvestrant based on the 2006 29th Annual San Antonio Breast Cancer Symposium presentation of the
which showed similar results for the 2 drugs, thus reserving high-dose estrogen, progestins, and androgens for later consideration. Additional clinical trials are needed to determine an optimal sequencing strategy and the role of the newer targeted therapies in combination with endocrine therapy.

For premenopausal women with metastatic breast cancer, both tamoxifen and ovarian function suppression, whether by surgery, radiation, or LHRH analogues, have established efficacy. Data from a randomized clinical trial showed that the combination of tamoxifen and an LHRH analogue, so-called total endocrine blockade, produced significantly better results, including better overall survival, than either agent alone. A small study has shown that after disease progression occurs in a patient taking an LHRH analogue plus tamoxifen, switching from tamoxifen to the AI anastrozole produces clinical benefit, defined as an objective response or disease stability for at least 6 months in 75% of patients. Data on the other endocrine agents for premenopausal women rendered biochemically postmenopausal are needed.

NEOADJUVANT OR PREOPERATIVE SYSTEMIC CHEMOTHERAPY

Chemotherapy in the preoperative setting was initially used for patients with inflammatory breast cancer and other inoperable breast cancers. Its use has expanded to patients with operable but locally advanced breast cancer, for which surgical resection may have been challenging in the past. With the use of chemotherapy before surgery, approximately a quarter of these patients have been shown to be able to undergo breast conservation. Additionally, now its use has expanded to patients with early-stage disease. The hallmark study that evaluated neoadjuvant chemotherapy is the NSABP B-18 trial, which enrolled patients with operable breast cancer (stage I and II) and stratified them by age, clinical tumor size, and clinical nodal status. Patients were randomized to undergo either surgery first followed by 4 cycles of doxorubicin-cyclophosphamide chemotherapy and tamoxifen (if appropriate) or 4 cycles of doxorubicin-cyclophosphamide chemotherapy up front followed by operation and tamoxifen (if appropriate). This study showed that the DFS and overall survival were similar in both groups. The local recurrence rate was also similar between the 2 groups: 7.6% in patients receiving postoperative chemotherapy and 10.7% in those receiving preoperative chemotherapy. The lumpectomy rate was increased from 60% to 68% with the use of neoadjuvant chemotherapy. As a result, breast-conserving therapy became possible in 20% of the 40% of patients who were not initially eligible for breast conservation.

The criteria for breast conservation surgery after neoadjuvant chemotherapy include a solitary residual tumor smaller than 5 cm, absence of skin or chest wall fixation, absence of a contraindication to breast radiation, and the patient’s desire for breast conservation surgery. Exclusion criteria include diffuse calcifications, inability to obtain negative margins, multicentric disease, residual skin changes, or significant residual volume of disease after chemotherapy.

The response to chemotherapy is documented for clinical response, which is classified as complete response (no residual disease clinically), partial response (>50% tumor reduction), minor response (<50% tumor reduction), no change, or disease progression. Studies have shown that approximately 30% of patients will have a complete response, 44% a partial response, 17% stable disease, 3% no change, and 2% disease progression.

The clinical response after neoadjuvant chemotherapy has been shown to predict DFS and overall survival. Therefore, therapies are being evaluated in clinical trials to determine which therapies can provide the highest clinical response rates.

Responses to chemotherapy before surgery are not uniform. Patients who have a complete response will have absolutely no evidence of residual disease; however, patients with a partial response may have either a small residual nidus of tumor in the center of the original tumor location or in some cases residual scattered cells that cover the original volume of the initial index tumor. Neoadjuvant chemotherapy has no impact on the reexcision rates for negative margins and has been shown to reduce the volume of breast tissue resected in patients with operable breast tumors. A smaller volume of tissue resected results in improved cosmesis after breast conservation surgery.

Pathological evaluation after surgery will reveal whether there has been a true pathological complete response, defined as no residual invasive breast cancer in the breast or axilla, or will report on the extent of residual disease in the breast and axilla. Patient treatment is based on clinical stage before receiving neoadjuvant chemotherapy, not on the pathological stage at the time of resection. Pathological complete response indicates improved patient survival.

As advances are made with therapy for breast cancer, pathological complete response rates have increased. A recent study that evaluated trastuzumab (Herceptin, Genentech, Inc, South San Francisco, CA) in the neoadjuvant setting for patients with HER2/neu-positive operable breast cancer at the M.D. Anderson Cancer Center found a 65% pathological complete response rate in patients receiving neoadjuvant trastuzumab along with paclitaxel and fluorouracil, epirubicin, and cyclophosphamide (FEC) chemo-
therapy. Further research is needed to determine whether this high level of pathological complete response can be corroborated.

Multiple national studies that are evaluating neoadjuvant chemotherapy and neoadjuvant hormonal therapy are under way. The American College of Surgeons Oncology Group Z1031 is a national study that is currently accruing patients for a head-to-head comparison of neoadjuvant exemestane, letrozole, and anastrozole in postmenopausal women with clinical stage II and III estrogen receptor–positive breast cancer. This trial randomizes patients to 1 of the 3 AIs for 16 to 18 weeks before surgery and will evaluate which of these 3 AIs results in the greatest clinical response. The basis for interest in the use of preoperative AI therapy is the high level of benefit seen in postmenopausal women in this setting.

The American College of Surgeons Oncology Group Z1041 is a national study that will be opening later in 2007, randomizing patients with HER2/neu–positive operable breast cancer to either neoadjuvant FEC followed by paclitaxel and trastuzumab or paclitaxel and trastuzumab followed by FEC and trastuzumab. Neoadjuvant chemotherapy allows the clinician and the patient an in vivo assessment of the tumor’s response to the chemotherapeutic agents the patient is receiving. If the tumor is not responding to the chemotherapy, the regimen can be changed to an alternative regimen that may be more effective on that particular patient’s tumor. Clinical trials of neoadjuvant therapy can answer important questions, allowing assessment of the best therapeutic agent for patients with breast cancer.

TAMOXIFEN PHARMACOGENETICS

The concepts that underlie pharmacogenetics first originated many years ago from the clinical observation that administration of the same dose of a given drug could result in marked variability in efficacy and toxicity. This observation was followed by the realization that inheritance could be a major factor responsible for that variance. One of the emerging examples of the importance of pharmacogenetics in the field of oncology is tamoxifen and the CYP2D6 enzyme system.

Tamoxifen represents an excellent example of a prodrug, a drug that requires metabolic activation to fully elicit its pharmacological effect. Whereas tamoxifen is considered a weak antiestrogen, the hydroxylated metabolites, 4-hydroxytamoxifen and 4-hydroxy-N-desmethyl tamoxifen, have 100-fold greater affinities for the estrogen receptor and up to 100-fold greater potency in suppressing estrogen-dependent cell proliferation compared with the parent drug. 4-Hydroxy-N-desmethyl tamoxifen, which is formed by the CYP2D6-mediated oxidation of N-desmethyl tamoxifen, is the most important of the 2 hydroxylated metabolites, given that steady-state concentrations range up to 20-fold higher than 4-hydroxytamoxifen. Jin et al and others have demonstrated in a prospective trial that both CYP2D6 genetic variation and inhibition of the enzyme system significantly affect the plasma concentrations of 4-hydroxy-N-desmethyl tamoxifen.

Although nearly 10% of white women inherit genetic variants that lead to the absence of functional CYP2D6 enzyme, an even larger group may be at risk for treatment failure, given the widespread use of CYP2D6 inhibitors such as the serotonin selective receptor inhibitors, which are widely prescribed for the treatment of tamoxifen-induced hot flashes and depression. This hypothesis was supported by data derived from a retrospective analysis of a randomized cooperative group adjuvant tamoxifen trial. The absence of functional CYP2D6, due to either homozygosity for a CYP2D6 null allele (*4) or the coadministration of a potent CYP2D6 inhibitor (eg, fluoxetine), was associated with a 3-fold higher risk of breast cancer recurrence compared with extensive metabolizers (defined as patients homozygous for the wild-type allele) who were not administered a CYP2D6 inhibitor (P= .007). Furthermore, we demonstrated an immediate broad peak in the relapse-free survival hazard rate for patients with impaired CYP2D6 metabolism. The hazard rate in the patients with extensive CYP2D6 metabolism was reduced and did not peak until nearly the fourth year. These findings lend support to our hypothesis that the peak seen in the hazard rate for recurrence after the initiation of tamoxifen may simply be secondary to a subset of patients unable to fully activate tamoxifen to its active hydroxylated metabolites.

The CYP2D6 pharmacogenetic research relating to tamoxifen was reviewed by the FDA Advisory Committee for Pharmaceutical Science on October 18, 2006. A unanimous recommendation was made for a change to the tamoxifen label to include a warning related to the increased risk of breast cancer recurrence for women with altered CYP2D6 metabolism. The final FDA label change is pending at this time.

Perhaps one of the most important areas for the translation of tamoxifen pharmacogenetics is in the setting of third-generation AIs. Large randomized trials have repeatedly showed that AIs, when administered after 5 years of tamoxifen therapy and after 2 to 3 years of tamoxifen therapy, significantly prolong DFS and overall survival. In contrast, the benefit of AIs over tamoxifen in the up-front setting is not associated with a survival benefit, and the absolute risk reduction is much less. We believe that the determination of CYP2D6 metabolism may identify a large group of patients who should preferentially
receive tamoxifen for several years before being switched to an AI. Studies are ongoing to determine the answers to these questions in the context of completed tamoxifen and AI trials.

ADJUVANT ANTI-HER2 THERAPY: NEW DATA

Recent results that incorporate anti-HER2 therapy as part of adjuvant treatment of patients with resected breast cancer are founded on optimal patient selection based on clinical characteristics and tumor biomarkers of response. In view of the challenges of accuracy of HER2 testing, several new initiatives have been performed to offer guidelines for testing. The essence of these recommendations include quality control using either immunohistochemical analysis to evaluate for protein overexpression or fluorescence in situ hybridization for evaluation of gene amplification.

UPDATE OF RESULTS OF MAJOR ADJUVANT TRASTUZUMAB STUDIES

The ongoing North Central Cancer Treatment Group N9831 Intergroup and NSABP B-31 adjuvant trials evaluated the role of adding trastuzumab to the doxorubicin (Adriamycin), cyclophosphamide, and paclitaxel (Taxol) regimen in patients with resected node-positive or high-risk node-negative breast cancer (B-31 enrolled patients with node-negative disease only) that overexpress or amplifies HER2. The Herceptin Adjuvant trial is evaluating adjuvant trastuzumab after completion of chemotherapy (with or without radiation). The Breast Cancer International Research Group 006 adjuvant trial evaluated the benefit of 2 trastuzumab-based regimens in HER2-amplified breast cancer and included 2 anthracycline-containing arms. Recently, reported data from these trials have demonstrated impressive DFS (in all the trials) and overall survival (in the joint analysis of N9831 and B-31) with benefits from adjuvant chemotherapy-trastuzumab vs chemotherapy only.

OPTIMAL DURATION OF ADJUVANT TRASTUZUMAB

The ideal duration of trastuzumab administration is being investigated, although most of the beneficial data reported so far are based on 1-year therapy. The Herceptin Adjuvant trial will provide comparative information for 1 vs 2 years of trastuzumab use. Recent provocative data in a small number of patients suggest that even short-term trastuzumab therapy may be effective in preventing recurrence. The results of the recently reported Finland Herceptin (FinHer) adjuvant therapy trial show that trastuzumab plus a taxane or vinorelbine for 9 weeks followed by three 3-weekly cycles of FEC is well tolerated and effective in preventing recurrence of ErbB2-amplified breast cancer.

At a median follow-up of 37 and 35 months for the trastuzumab and nontrastuzumab groups, respectively, the addition of 9 weeks of trastuzumab to an adjuvant chemotherapy regimen prevented any breast cancer recurrence (hazard ratio, 0.42; P = .01) and improved 3-year DFS (hazard ratio, 0.29; P = .002). A trend was seen toward improved overall survival (hazard ratio, 0.41; P = .07). However, the 95% confidence interval for the hazard ratio for recurrence-free survival was wide (0.21-0.83) and based on only 27 events in the 2 nontrastuzumab arms and 12 events in the 2 trastuzumab arms. The question of shorter duration of trastuzumab therapy of less than 1 year is now being addressed by the French Breast Group, in a trial initiated in 2006. These investigators plan to enroll 8000 women to receive either 6 months or 12 months of trastuzumab therapy after completing chemotherapy and radiation as indicated.

ADDITIONAL ANTI-HER2 STRATEGIES BEYOND TRASTUZUMAB

Despite the impressive results of the recently released trastuzumab adjuvant therapy trials, 15% of patients with HER2 overexpressing or amplified breast cancer developed tumor relapse at 3 years, and some concern has arisen related to site-specific metastases, including brain. Several pan-HER or dual HER inhibitors are at different stages of development, but lapatinib is the most advanced. Lapatinib is a reversible tyrosine kinase inhibitor that potently inhibits both ErbB1 and ErbB2 tyrosine kinase activity. In breast cancer cell lines treated with lapatinib, growth arrest and cell death were observed. Lapatinib also selectively inhibits tumor xenograft growth in a dose-dependent manner. In a pilot study conducted in patients with metastatic tumors that overexpress ErbB2 and/or ErbB1, biopsy specimens from responders treated with lapatinib exhibited increased apoptosis, whereas specimens obtained from nonresponders did not.

Lapatinib has undergone preclinical, phase 1, pharmacokinetic, and phase 2 and 3 evaluation in the setting of HER2-positive metastatic breast cancer, with impressive resulting data. Results of 3 phase 1 monotherapy studies in cancer patients showed that lapatinib was generally well tolerated, with most the common adverse events being diarrhea, nausea and vomiting, anorexia, fatigue, and rash.

Although both trastuzumab and lapatinib inhibit the same receptor, ErbB2, the combination is potentially attractive because each agent targets a different part of the receptor. Trastuzumab targets the extracellular domain and lapatinib the intracellular domain. In addition, they appear to have different mechanisms of action, with trastuzumab activity at least in part due to increased internalization and degradation of ErbB2 and lapatinib inhibiting the ErbB2 tyrosine kinase. This differentiation may lead to sustained
inhibition of activation of the receptors and possibly to enhanced inhibitory signals. When combined with trastuzumab in breast cancer cells, lapatinib enhances apoptosis and inhibits transactivation of ErbB3 to a greater extent than either agent alone. Moreover, the effect of combined lapatinib plus trastuzumab on mediators of cell survival, notably in ErbB2-overexpressing breast cancer cell lines, was found to be greater than that of gefitinib (an inhibitor of HER1, the epidermal growth factor receptor) plus trastuzumab.\textsuperscript{82,83} Ongoing studies are evaluating cardiotoxicity due to lapatinib.

**UPCOMING ADJUVANT STUDIES TARGETING THE HER2 AND OTHER PATHWAYS**

Trials that incorporate adjuvant lapatinib are being developed on a worldwide basis. The Adjuvant Lapatinib and/or Trastuzumab Trial Organization is an 8000-patient, early-HER2+ study that will evaluate trastuzumab alone, lapatinib alone, or sequential vs concurrent use of these agents. Strong correlative studies are part of this global trial.\textsuperscript{84} In addition to trials that optimize blockade of the HER2 pathways, other approaches for future trials include antiangiogenesis agents or agents that may be involved in modulation of resistance to trastuzumab and/or lapatinib. Safety and quality-of-life issues will also be an important part of new studies.

Another trial under way is the Tykerb Evaluation After Chemotherapy study, a randomized phase 3 trial of lapatinib vs placebo in women with early-stage breast cancer who have not received trastuzumab for any number of reasons.

**CONCLUSION**

The field of epidemiology has traditionally evaluated whether lifestyle factors are associated with breast cancer risk. However, with an increased understanding of the molecular processes that underlie carcinogenesis in the context of mapping of the human genome, the field of molecular epidemiology has emerged. We are moving closer to being able to determine whether an inherited variation in genes that regulate cellular homeostasis affects cancer risk. The ultimate goal of molecular epidemiology is to personalize risk assessment, allowing a more precise estimate of which patients are at higher risk for development of cancer. In these patients, more intensive screening, chemoprevention, or prophylactic surgery may ultimately reduce the morbidity and mortality associated with breast cancer.

Breast cancer management has become increasingly complex, requiring that physicians integrate the data from the patient’s history along with new imaging modalities, genetics, and biomarkers to develop a treatment plan for both the prevention and treatment of breast cancer. The introduction of microarray technology has allowed scientists to query the expression of thousands of genes from an individual tumor. This technology has been used to discover novel genes or sets of genes in which the pattern of gene expression can be used within the context of a clinical setting (eg, women with surgically resected early-stage breast cancer) to discover genes associated with a clinical outcome of interest (eg, recurrence or survival).

Because breast cancer management continues to evolve rapidly, a multidisciplinary approach is required to implement a comprehensive treatment plan for both the prevention and treatment of breast cancer. It is in this setting that the ultimate goal of reducing the incidence, morbidity, and mortality of this disease is best achieved.

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