Preliminary Data from Ongoing Adjuvant Aromatase Inhibitor Trials

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Abstract

With recent results showing letrozole and anastrozole to be superior to tamoxifen as initial therapy for advanced disease, the aromatase inhibitors are poised to establish their place in the adjuvant therapy of postmenopausal receptor-positive breast cancer. A review of the rationale, design, and preliminary results of the ongoing adjuvant trials that include aromatase inhibitors will be presented, along with the ongoing or planned substudies. Two strategies employing aromatase inhibitors after tamoxifen are being evaluated. The MA.17 international intergroup trial is randomizing postmenopausal patients who are disease-free after 5 years of adjuvant tamoxifen to an additional 5 years of letrozole or placebo. In a similar design, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B33 trial is randomizing this patient population to 2 years of exemestane or placebo after the standard 5 years of adjuvant tamoxifen. The second approach under study is the use of both aromatase inhibitor and tamoxifen in sequence within the first 5 postoperative years. The International Cancer Collaboration Group (ICCG) trial is comparing 2 years of exemestane after 3 years of tamoxifen to a standard 5-year course of tamoxifen. Similarly, the ARNO trial is comparing 5 years of tamoxifen versus 2 years of tamoxifen followed by 3 years of anastrozole. In a four-arm study Breast International Group/Femara-Tamoxifen (BIG/FEMTA) conducted by the BIG, one arm contains letrozole given for 3 years after 2 years of tamoxifen. Several trials are investigating the role of anastrozole, letrozole, or exemestane as a 5-year adjuvant therapy to replace the standard 5 years of tamoxifen. Only the Arimidex and Tamoxifen, Alone or in Combination (ATAC) trial is testing a 5-year combination of tamoxifen plus an aromatase inhibitor in this setting. Companion studies of effects on end-organs other than the breast are ongoing in a number of these trials. Aromatase inhibitors are poised to alter the treatment paradigm of breast cancer and hopefully improve outcome for a substantial number of patients.

Introduction

The growth of hormone receptor-positive breast cancer can be altered clinically by several classes of agents that antagonize the effects of estrogen (1). The SERMs, exemplified by tamoxifen, constitute one such class of drugs. Pure antiestrogens such as fulvestrant (Faslodex) also exert a potent antiestrogenic effect and show efficacy in tamoxifen-resistant cell lines in preclinical models. Thus, unlike tamoxifen, which exerts both an agonist and an antagonist effect, fulvestrant is a pure antagonist and acts by down-regulating ER content (2).

Aromatase (estrogen synthetase) inhibitors antagonize the action of estrogen by reducing its levels both in the circulation and in normal and malignant breast tissue (3). They were initially tested in postmenopausal women with breast cancer progression after tamoxifen treatment. A superior outcome with these drugs compared to either megestrol acetate or aminoglutethimide resulted in their becoming the established second-line treatment for ER-positive metastatic breast cancer (4–13). More recently, three of the selective third-generation inhibitors, anastrozole, letrozole, and exemestane, have been compared to tamoxifen in the same setting (14–17). On the basis of both improved efficacy and superior side effect profiles, aromatase and letrozole have now been approved for use as first-line treatment for women at first relapse of their disease. These data are reviewed in detail elsewhere in this journal issue (18, 19).

Although useful in the treatment of advanced disease, the real benefits of tamoxifen have been seen in its ability to reduce mortality by as much as one-third for up to 15 years after primary surgery in women given 5 years of adjuvant treatment. This makes tamoxifen one of the most successful anticancer therapies ever developed in terms of “number of years of life saved.” The recently demonstrated superiority of the aromatase inhibitors over tamoxifen in the advanced disease setting is, therefore, a significant finding. Consequently, they are currently being tested in the adjuvant setting in women with early-stage breast cancer, and the results promise to alter the current treatment paradigm of the disease. The trials that are ongoing and their companion studies are briefly described.

Rationale and Design of Ongoing Adjuvant Trials

Biological and Pharmacological Concepts: Disease “Resistance” Mechanisms. After initially responding to tamoxifen, metastatic breast cancer inevitably begins to progress de-

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3 SERM, selective ER modulator; ER, estrogen receptor; BMD, bone mineral density; NSABP, National Surgical Adjuvant Breast and Bowel Project; NCIC, National Cancer Institute of Canada; CTG, Clinical Trials Group; ATAC, Arimidex and Tamoxifen, Alone or in Combination (trial).
Aromatase Inhibitors in Early Breast Cancer

Despite ongoing therapy, on occasion, withdrawal of tamoxifen in this circumstance results in further clinical remission—a phenomenon termed tamoxifen resistance or “dependence” (20, 21). Further credence has been lent to this concept by the observation in the NSABP B14 trial and in a Scottish adjuvant trial (22, 23) that patient outcome is worse if tamoxifen therapy is continued beyond 5 years of treatment. This has resulted in 5 years of tamoxifen becoming the standard duration of treatment in the adjuvant setting.

Several theories have been offered as to the mechanism of tamoxifen resistance. First, mutation of the ER has been demonstrated in MCF-7 cells, resulting in estrogen hypersensitivity when passaged in estrogen-deprived media (20). This potentially results in tamoxifen exerting an estrogen agonistic effect. It has been postulated that this may be enhanced by increasing metabolism of tamoxifen to metabolites with weak estrogen agonist action. In addition, hypersensitivity to residual estrogen may occur (Fig. 1). In vivo experiments have also shown that MCF-7 cells in nude mice initially regress in response to tamoxifen but are later stimulated by its weak estrogen agonist properties (24). Secondly, estrogen-deprived MCF-7 cells develop up-regulation of aromatase, which may in turn result in increased autocrine stimulation by estrogen (20). In principle, tamoxifen might have the same effect. Thus, theoretically, cessation of tamoxifen in a patient with disease progression, followed by the initiation of an aromatase inhibitor, might simultaneously withdraw tamoxifen’s estrogen agonist effect and deplete both locally produced and circulating estrogen, to which the disease may be exquisitely sensitive (20, 21).

Alternatively, breast cancer may be treated initially by an aromatase inhibitor, and tamoxifen or other endocrine therapy reserved for second-line treatment. Use of an aromatase inhibitor as first-line therapy is supported by the recent demonstration of superior outcomes both in first-line therapy and in the neoadjuvant setting (25). Finally, combination therapy with an inhibitor and tamoxifen is a therapeutic option that in principle may overcome the development of resistance by several of the mechanisms outlined above (Fig. 1). However, stimulation of a “hypersensitive” receptor by exogenous estrogens or the agonist effects of tamoxifen and/or its metabolites would remain theoretical mechanisms of resistance to this “total estrogen blockade” strategy with combination therapy (Fig. 1).

Pharmacological Considerations. Pharmacological interaction between endocrine therapies may interfere with efficacy and disease outcome. Timing may be critical in switching from one treatment to another. For example, cells that have developed one or more of the resistance mechanisms outlined above may be eradicated by subsequent therapy, provided the switch is made promptly and the appropriate therapeutic doses are given. Potential problems exist with both of these requirements. First, drug interaction with tamoxifen results in a reduction in tamoxifen’s plasma levels of letrozole and anastrozole to 62.4% (26) and 73% (27), respectively. It has been proposed that these small differences would unlikely be of importance, although they might be in the presence of a hypersensitive receptor capable of being stimulated by very low picomolar concentrations of estrogen. In addition, tamoxifen and its metabolites have very long half-lives and tissue binding (28), and by definition any switch from tamoxifen to an aromatase inhibitor would involve a degree of combination therapy for a significant period. This could have therapeutic implications.

Design of Ongoing Adjuvant Trials. A number of the trials are comparing an arm containing an aromatase inhibitor given for 5 years against a standard 5 years of tamoxifen as immediate postoperative adjuvant therapy. The investigational arm of these trials, which similarly are all given for 5 years, include the following configurations: an aromatase inhibitor, tamoxifen followed by an inhibitor, an inhibitor followed by tamoxifen, and the combination of an inhibitor with tamoxifen. A second set of trials are being conducted in which patients completing 5 years of adjuvant therapy are enrolled on study to either 5 or 2 years of inhibitor or placebo. A brief update of...
these trials as of June 2001 is given below. The primary end points of these trials include disease-free and overall survival, and although secondary end points differ, they include the incidence of new contralateral primary tumors. In all of the trials, the once-daily dose of tamoxifen is 20 mg and of letrozole is 2.5 mg.

**Letrozole-containing Trials**

**BIG/FEMTA (Breast International Group/Femara-Tamoxifen).** This study has 4 arms, each running for 5 years: tamoxifen; letrozole; tamoxifen for 2–3 years followed by letrozole for 2–3 years; and letrozole for 2–3 years followed by tamoxifen for 2–3 years. The trial started in 1999 and has enrolled 3672 patients of a planned sample size of 5310. The two monotherapy arms of the trial have been fully accrued for some time, but it is unclear whether these results will be presented independently before the final analysis of all four arms. This is the only trial being conducted that examines the sequence of inhibitor given prior to tamoxifen. No companion trials have been conducted as yet, but both bone and lipid metabolism substudies are under consideration.

**JMA.17.** This study is an intergroup study being led by the NCIC CTG and includes members of the North American Intergroup including Cancer and Acute Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), North Central Cancer Treatment Group (NCCTG), Southwest Oncology Group (SWOG), European Organization for Research and Treatment of Cancer (EORTC), International Breast Cancer Study Group (IBCSG), and United Kingdom participants. The trial was initiated in 1998 and has enrolled 3017 patients with a planned accrual of 4800. The median age of the participants to date is 63 years; 56% have had prior chemotherapy, and 46% had node-negative disease at their initial presentation. Hot flushes, sweating, and arthralgias are the most common side effects in patients on study. The main study contains two quality-of-life tools, the SF-36 and the MENQOL (menopausal-specific quality of life). Additionally, several substudies are under way. These include bone (n = 49/200) and lipid (n = 169/300) metabolism trials. The bone substudy is addressing whether women without osteopenia (BMD T score less than −2.0), taking daily calcium (500 mg) and vitamin D (400 IU), develop accelerated bone loss above those taking the supplements and placebo. End points of the bone substudy include bone biomarkers (serum bone alkaline phosphatase, serum C-telopeptide and urine N-telopeptide) and BMD; cholesterol, triglycerides, LDL, HDL, and Lp(a) are the measurable end points of the lipid substudy.

**Exemestane-containing Trials**

**“EXACT” Trial.** This study conducted by the ICCG (International Cancer Collaboration Group) compares 5 years of tamoxifen to 2–3 years of tamoxifen followed by 2–3 years of exemestane. The trial was activated in March 1999, and of 4400 patients, 4135 have been enrolled to date. Bone metabolism is being evaluated by BMD in a companion trial and quality of life using the FACT-ES (functional assessment of chronic therapy-endocrine symptoms) tool is being evaluated. Endometrial assessment by transvaginal ultrasound is also ongoing.

**NSABP B33.** This trial has only recently opened to patient accrual in May 2001 and is evaluating the outcome of patients randomized to 2 years of exemestane or placebo after 5 years of adjuvant tamoxifen. The planned sample size of the study is 3000 women. Bone, lipid, quality-of-life, and other substudies are planned.

**Tamoxifen versus Exemestane: Tamoxifen Exemestane Adjuvant Multinational (TEAM) Trial.** An additional head-to-head comparison of tamoxifen versus exemestane is planned. The study has recently opened and plans are to enroll 4400 patients. The substudies planned include endometrial changes, lipids, quality-of-life, and tolerability.

**Anastrozole-containing Trials**

**The ATAC Trial.** This is the largest adjuvant trial ever conducted in breast cancer patients. A total of 9366 patients were accrued between 1996 and 1999. Patients are now in follow-up, and the first report of the results is expected at the 24th Annual San Antonio Breast Cancer Symposium, December 10–13, 2001. Companion studies include bone metabolism as assessed by BMD, lipid metabolism, an endometrial evaluation study, pharmacokinetic interactions between tamoxifen and anastrozole, and a quality-of-life (FACT-ES) study.

Preliminary data from the pharmacokinetic study were presented at the 23rd Annual San Antonio Breast Cancer Symposium in December 2000 (27). The study evaluated drug concentrations (Cmin) of anastrozole, tamoxifen, and desmethyltamoxifen in patients who had been on study medication for >3 months. Drug levels of anastrozole were 27% lower in the presence of tamoxifen than in patients on anastrozole alone. Estradiol suppression in the anastrozole-alone arm versus the combination was, however, identical. The authors concluded that the modest suppression of anastrozole levels by tamoxifen is, therefore, clinically irrelevant. This is discussed further below. At the same meeting, the initial results from the substudy evaluating the endometrium were presented. Of 285 women studied with transvaginal ultrasound and hysteroscopy, 23% of women developed endometrial thickening of >5-mm thickness, and 8% had preexisting fibroids, polyps, and ovarian cysts (29).

**The ARNO Trial.** This study is being conducted by the ABCSG (Austrian Breast Cancer Study Group) in collaboration with the GABG (German Adjuvant Breast Cancer Group). In this trial, patients are randomized either to tamoxifen for 5 years or to 2 years of tamoxifen followed by 3 years of anastrozole. To date, 2300 patients of a planned sample size of 2500 have been enrolled. This trial was opened to accrual in October of 1996 and has accrued slowly primarily because the randomization occurs at the time of initial diagnosis rather than during clinical follow-up, as has been done in several of the other sequence trials. No companion trials are ongoing.

**Discussion**

The paradigm that tamoxifen with or without chemotherapy is the adjuvant treatment of choice for all breast cancer patients is likely to change in the next few years. The data that will be forthcoming from the trials described above in the next decade, starting with the first report from the ATAC trial, will be unprecedented both in terms of the extent of the data and the
speed with which these results will become available to oncologists. The efficacy of the aromatase inhibitors as a class of drugs in adjuvant therapy will be defined, and their appropriate sequence or combination with tamoxifen determined. Importantly, the ultimate clinical utility will depend not only on the efficacy against breast cancer but also on their tolerability and long-term effects on end-organs other than the breast. The provocation of vasomotor and urogenital symptoms will be important particularly for long-term use. Serious toxicities such as the endometrial cancer and venous thromboembolism seen with tamoxifen, although not expected, will require evaluation. As mentioned, the effect on bone and lipid metabolism and neurocognitive function will also be critical. Although the assumption that these drugs may cause bone resorption and elevation in cholesterol is widely held, it is important to recognize that the role of physiological estrogens in postmenopausal women is not understood, and this assumption may be incorrect. Moreover, important differences in this regard may become evident among different aromatase agents. Pharmacological interactions between tamoxifen and inhibitors lower the plasma concentration of the inhibitor and may be relevant in the setting of estrogen hypersensitivity. This could be particularly true if full therapeutic levels are needed for a cytotoxic effect at the time of the switch from one therapy to another. In addition, letrozole has a more impressive track record in both the preclinical and the metastatic setting than anastrozole. Its more complete suppression of estradiol and its better penetration into cells may yield important clinical differences. Exemestane as a steroid may have a positive effect on bone and lipid metabolism through androgenic action of the parent compound and its 4-hydroxy exemestane metabolite.

Many unanswered questions will remain at the conclusion of the current set of trials. For example, the optimal 10-year adjuvant treatment will be unclear if the inhibitors are superior to tamoxifen as initial therapy but also add a benefit after 5 years of tamoxifen. The optimal duration of treatment with the aromatase inhibitors may also not be defined, because more than 5 years might be superior to a 5-year exposure. If combination therapy in the ATAC trial is superior to monotherapy, it will open up the possibility of future combination therapy trials with newer SERMs or antiestrogens such as fulvestrant. These agents may also prove superior to tamoxifen when given in sequence with the aromatase inhibitors. If the combination arm of the ATAC trial is not superior, combination of a SERM that has less estrogen-agonist effects in the preclinical setting, such as toremifene, might be more suitable in an estrogen-deprived environment.

Finally, if the therapeutic index of aromatase inhibitors proves to be advantageous in the adjuvant setting in healthy postmenopausal women, then it opens up the possibility of exploring their use as breast cancer preventatives. The MA.17 trial, for example, if it is positive, will allow the possibility of women taking tamoxifen for prevention to use this agent in sequence after the FDA-recommended 5 years of tamoxifen therapy. We at the NCIC CTG, and others, are currently undertaking a number of chemoprevention pilot trials with aromatase inhibitors in women at increased risk of breast cancer. In addition, the IBIS II trial in women with ductal carcinoma in situ (DCIS), and at elevated risk of breast cancer, is scheduled to start in 2001. This trial will randomize postmenopausal women between tamoxifen, anastrozole, and placebo.

The application of the aromatase inhibitors to the treatment of breast cancer has proved to be an important step for women with breast cancer, and it is hoped that the adjuvant results will further improve their outcome.

Open Discussion

Dr. Angela Brodie: We have some data on using tamoxifen and then switching to letrozole back and forth before resistance develops. Thus far, it doesn’t really make any difference which you start with, going from letrozole to tamoxifen and back again or vice versa. But they’re not as good as just giving letrozole alone.

Dr. Per Lonning: I think one of the problems with these combinations of the SERM and aromatase inhibitor is that the previous clinical trials didn’t work. We know there was a drug interaction between aminoglutethimide and tamoxifen. On the other hand, the paper by Decensi (J. Clin. Oncol., 17: 2633–2638, 1999) 2 years ago showed that for all types of surrogate parameters, you got exactly the same effects with 5 mg of daily tamoxifen as with 20 mg. So it’s not like that drug interaction played a key role in suppressing tamoxifen levels. That raises some concerns to me, whether this concept would work.

Dr. Goss: I don’t think we can extrapolate from the metastatic setting to the adjuvant setting. Also, I don’t know if anyone else in the room thinks that we’ve truly satisfied ourselves that combination endocrine therapy isn’t going to work. I don’t think the combination of tamoxifen and aminoglutethimide is comparable to what we’re doing now with third-generation aromatase inhibitors.

Dr. Aman Buzdar: With anastrozole, that drug sat on the shelf for a long time because in a small animal toxicology study the drug cleared very quickly and they thought that it would have to be given several times a day. Maybe there are a number of other differences that we don’t know of; I think these animal data are very interesting, but clinical data will be the most relevant.

References

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