The Role of Tamoxifen and Aromatase Inhibitors/Inactivators in Postmenopausal Patients

Kathleen I. Pritchard
Toronto-Sunnybrook Regional Cancer Centre, University of Toronto, Toronto, Ontario M4N 3M5, Canada

Abstract
The traditional hormonal cascade of the 1970s and 1980s used tamoxifen followed by megestrol acetate and subsequently by aminoglutethimide. In the 1990s, however, three trials of third-generation aromatase inhibitors (AIs) compared with megestrol acetate and two trials of third-generation AIs compared with aminoglutethimide showed improved efficacy and decreased toxicity for the newer AIs. Thus, the hormonal cascade changed in the late 1990s, to one in which tamoxifen, followed by a third-generation AI, followed by megestrol acetate, seemed more suitable. Now, however, several trials comparing anastrozole, letrozole, and exemestane to tamoxifen as first-line hormonal agents for metastatic breast cancer have shown that these drugs are at least equivalent and perhaps superior to tamoxifen in that setting in terms of response rate and time to progression. Results from 1021 patients randomized to receive anastrozole versus tamoxifen showed a slightly improved overall response rate (RR; 29% versus 26%), slightly improved clinical benefit (CB; 57% versus 52%), and a significantly improved time to progression (TTP; 8.5 months versus 7.0 months) in favor of anastrozole. In 907 women randomized to treatment with letrozole versus tamoxifen, significantly improved RR (30% versus 20%), CB (49% versus 38%), and TTP (9.4 months versus 6 months) have all been shown for those treated with letrozole. In addition, a randomized Phase II trial of 121 patients has shown nonsignificant benefits in favor of exemestane (RR 41% versus 14%; CB 56% versus 42%; TTP not available). To date, none of these trials has demonstrated any overall survival benefit. Additional follow-up in regard to survival in the trial of tamoxifen versus letrozole and an expanded Phase III trial of tamoxifen versus exemestane are ongoing.

Introduction
Hormonal therapy remains a mainstay in the treatment of women with metastatic breast cancer. However, the use of hormonal agents for metastatic breast cancer in postmenopausal women deserves re-examination at this time. Initially, estrogens, in particular diethylstilbestrol, were used as first-line therapy in the treatment of postmenopausal women with metastatic breast cancer. This treatment was initially tried on all postmenopausal women, but with the elucidation of its mechanism of action by way of the ER (1), physicians began to select patients for endocrine therapy on this basis. It has been shown repeatedly that women whose tumors overexpress ER and/or PgR are more likely to respond to endocrine therapies of any type. In particular, women whose tumors are positive for ER or PgR have response rates of ~30%, while those whose tumors have high levels of both receptors may have response rates as high as 60% or 70% to any hormonal approach. Higher levels of ER and PgR are closely correlated to response (2).

In the 1970s and 80s the traditional hormonal cascade for postmenopausal women involved tamoxifen followed by a progestational agent such as megestrol acetate (Megace) or medroxyprogesterone acetate (Provera), and subsequently aminoglutethimide, the prototype aromatase inhibitor. More recently, however, the results of a number of trials of third-generation AIs compared with previous standard therapy in second-line and now in first-line treatment of metastatic disease have changed this approach dramatically.

The AIs and Their Historical Development
Aminoglutethimide, the prototype AI, was originally developed as an anticonvulsant. It was first identified as an inhibitor of adrenal steroidogenesis in 1967 and first used as a form of medical adrenalectomy in 1970. Aminoglutethimide was introduced into clinical practice for advanced breast cancer in 1981. This drug, like the second- and third-generation AIs, acts by inhibiting the aromatase enzyme, the key enzyme mediating the transformation of androstenedione and testosterone to estrone and estradiol. Since this aromatization process is the main source of estrogen in postmenopausal women, aromatase inhibition dramatically reduces estrogen levels in such patients.

Aminoglutethimide was in many ways a poor AI for clinical use in that it is not particularly specific. It inhibited not only aromatase but also the 17, 11, and 21 hydroxylation pathways of adrenal steroidogenesis, resulting in reduced levels of the glucocorticoids and mineralocorticoids necessary for healthy life. Thus, aminoglutethimide given in doses of more than 250–500 mg daily required supplemental prednisone and/or fludrocortisone in order to avoid adrenocortical insufficiency syndromes. The second-generation AIs, such as formestane, were the next important development. Formestane is a much more specific AI,

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2 To whom requests for reprints should be addressed, at Toronto-Sunnybrook Regional Cancer Centre, University of Toronto, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada. Phone: (416) 480-4616; Fax: (416) 480-6002; E-mail: kathy.pritchard@tsrcc.on.ca.
but because it was available only in an injectable form, it was not the ideal AI for clinical use.

Subsequently, two groups of third-generation AIs were developed. These include the nonsteroidal inhibitors anastrozole (Arimidex), letrozole (Femara), and vorozole (no longer in commercial development), as well as the steroidal AI exemestane (Aromasin). The nonsteroidal inhibitors bind to the heme part of the aromatase enzyme in a reversible fashion, while the steroidal inhibitors bind to the substrate binding site of the enzyme in an irreversible fashion and are, therefore, often referred to as aromatase inactivators (3).

Trials of Third-Generation AIs in Second-/Third-Line Therapy for Metastatic Disease

There are now six randomized trials of the third-generation AIs as second- and third-line therapy, four comparing an AI to megestrol acetate and two comparing an AI to aminoglutethimide. These trials and their results are summarized on Table 1. More than 2250 women have been randomized to comparisons of third-generation AIs versus megestrol acetate (4–7). Superior outcomes of one type or another (OS, TTF, TTP, RR) were shown in several of these studies. In addition, >900 women were randomized to studies of the second-generation AIs versus aminoglutethimide (500 mg without prednisone). The new AIs were shown to be superior for several outcomes in several of these trials as well (8, 9).

In addition, several Phase III trials comparing third-generation AIs head-to-head in postmenopausal women having failed tamoxifen are underway. A study conducted by Novartis has compared anastrozole with letrozole in >650 women with measurable or assessable lesions using TTP, RR, TTF, and OS as endpoints. Results are not as yet available. In addition, an ongoing study conducted by Pharmacia is comparing anastrozole to exemestane in women with measurable visceral lesions. More than 200 women have entered this study for which the stated endpoints are RR, TTP, OS, and tolerability. Once again, no results have as yet been published or presented.

Trials of Third-Generation AIs in First-Line Therapy for Metastatic Disease

There are essentially three trials in which women with ER- and/or PgR-positive or ER- and PgR-unknown tumors, disease-free interval ≥1 year, and an adjuvant tamoxifen-free interval of 6–12 months or greater, have been randomized after relapse to tamoxifen versus a third-generation AI (anastrozole, letrozole, or exemestane).

The trial of anastrozole versus tamoxifen actually consists of two large, randomized trials of identical design, one carried out in North America and one in Europe. These trials were designed to be analyzed in combination. In the two trials combined, 1021 patients were randomized to receive either anastrozole or tamoxifen (10, 11). The letrozole trial was run as one large trial in which 907 women were randomized to treatment with letrozole versus tamoxifen (12). The exemestane trial was a randomized Phase II trial with a plan to extend to a larger Phase III trial (13, 14). To date, 120 patients have been randomized to this trial, which is now expanding its accrual in Europe and Canada. Table 2 displays the characteristics of the patients in these trials in terms of ER and PgR positivity, numbers with visceral disease, numbers with previous tamoxifen exposure, and numbers having received previous chemotherapy.

Table 3 displays the major outcome measures from each study by treatment arm. As demonstrated, RR, CB, and TTP were superior for the AIs in each study but only significantly so for TTP in the studies comparing anastrozole with tamoxifen and for RR, CB, and TTP in the study comparing letrozole with tamoxifen. The exemestane versus tamoxifen study, although suggesting large differences in OR and CB, had so few patients that significance cannot be determined. Considerable discussion has surrounded the differences between the European and the American anastrozole versus tamoxifen studies and the differences in their patient populations. The North American study suggested a significant difference in TTP and in CB in favor of anastrozole, while the European study did not. Although a much
higher proportion of the North American patients were known to be ER- and PgR-positive, the patients with ER and PgR status unknown in the European study were likely quite similar to the North American patients, so that the lack of measurement of ER and PgR status in some women in the European study does not likely explain these small differences. Hopefully, these ER and PgR data can be retrospectively obtained so that this matter can be clarified.

Table 3 shows some interesting toxicity data. These data suggest that thromboembolic disease is slightly more common in patients randomized to tamoxifen than anastrozole, as perhaps are gastrointestinal disturbances and lethargy. Hot flashes, however, seem equally common in women in both arms. No tests of significance have been applied to these toxicity differences because of concern about multiple testing.

The letrozole versus tamoxifen trial had a somewhat different design in that a crossover to the other compound was built into the design of this trial. The primary endpoint was TTP. Patients studied appear very similar to those in the anastrozole trial. In particular, the percentages with ER-positive versus unknown receptor status for this trial and for the pooled anastrozole versus tamoxifen trials are virtually identical. The results of the letrozole versus tamoxifen trial are somewhat more striking in that TTP, TTF, RR, and CB were all highly statistically significantly better for letrozole.

Survival data are not yet available from either the exemestane or the letrozole trial and are awaited with interest.

The study of exemestane versus tamoxifen, while preliminary, also suggests that there could be a benefit in favor of exemestane. In addition, the extensive data showing an 8% RR and a 24% CB for exemestane in patients who have failed previous AIs, including aminoglutethimide and third-generation AIs, are also impressive (15). Such data have, however, not been collected in such a systematic fashion for letrozole or anastrozole, so that the clinical superiority of exemestane in this regard is really unknown. Clearly more data comparing exemestane with tamoxifen and comparing the various AIs directly with one another would be very useful.

In summary, however, it seems that both letrozole and anastrozole are at least as good and probably better than tamoxifen for first-line therapy of metastatic disease. For anastrozole, perhaps only TTP is superior; however, while for letrozole, every major endpoint reported to date shows superiority. Clearly the direct comparison trial between anastrozole and letrozole will provide additional interesting data.

Thus, it seems appropriate for women with hormonally responsive disease to begin therapy with an AI. Tamoxifen may still be acceptable first-line therapy in this setting, however, particularly if issues of cost or drug availability are paramount. There is to date no data suggesting that prescribing such patients tamoxifen first and moving to an AI as second line is detrimental to their overall survival.

Clearly, additional results from ongoing trials, including those in the adjuvant setting, will shed additional light in these areas. It will also be interesting to follow the upcoming comparisons of fulvestrant (Faslodex) to tamoxifen since this “pure” antiestrogen has already been shown in randomized trials to be at least equivalent to anastrozole in patients whose tumors have already progressed on tamoxifen.

Open Discussion

Dr. Kent Osborne: These are relatively small trials, although they may have 200 or 300 patients in each arm. The largest trial is the Femara and tamoxifen trial, and it does show more consistency. If you look at all those trials, the fulvestrant versus Arimidex, the Arimidex versus Megace, and all those trials, it’s always trending. A couple of months could be better. It’s just not statistically significant. If you double the patient size, it probably would be, and you’d have more consistency.

Dr. Pritchard: Overall, though, if you look at more than 1000 patients in the two anastrozole trials rolled together, you don’t see consistent changes in the end points; it’s probably just the opposite end of the same confidence interval. I personally remain fairly unconvinced that there are real differences clinically among these third-generation aromatase inhibitors.
Dr. Matthew Ellis: If you look at the number of patients who progress on these trials in 3 months in the second-line setting, it’s about 50%. In the first-line setting, it was about 30%. Metastatic disease is a tough setting in which to develop endocrine therapy drugs because there’s so much resistance. There may be very important differences between different classes of drugs that could be critical in the adjuvant or prevention setting. You may not see it in the metastatic disease setting because the disease doesn’t care about estrogen at that point.

Dr. Pritchard: That’s why it is great that we’ve gone on to do some big studies in the adjuvant setting, and I think the data may be much more reliable.

Dr. Per Lonning: I agree with you that very many patients don’t respond to any type of therapy, particularly when they come to the second-line treatment, but in general you see improved duration of the response with all these novel compounds. I think all of us believe that one of the key reasons why these new drugs have shown superiority is that they are more potent biochemically. With the comparison of anastrozole and letrozole, the question will be how that fits with the biochemical data. In our head-to-head comparison, letrozole is much more potent compared to anastrozole, both with respect to aromatase inhibition and estrone sulfate suppression. Another interesting question is the lack of cross-resistance between the compounds, because there are five different trials to show the lack of cross-resistance between a steroidal and a nonsteroidal. Contrary to common belief, it goes both ways, and this lack of cross-resistance even obtains if you use a less potent compound after the more potent one up front. So it relates to difference in the mechanism of action of the drugs.

Dr. Anthony Howell: If I might make two comments, one is that the mistake is to do two trials. When you do one on one side of the Atlantic and one on the other side of the Atlantic, you always get different results. For example, letrozole was highly effective compared to megestrol acetate where I come from, whereas in the States there was no difference between megestrol acetate and letrozole. But the second issue is the Fuqua mutation and how it might relate to responsiveness, which potentially can change the whole way we look at aromatase inhibitors. It may be that those extra picomoles, as Kent Osborne said earlier today, are tremendously important.

References
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