Impact of Tamoxifen on the Pharmacokinetics and Endocrine Effects of the Aromatase Inhibitor Letrozole in Postmenopausal Women with Breast Cancer¹


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ABSTRACT

This study examined whether the addition of tamoxifen to the treatment regimen of patients with advanced breast cancer being treated with the aromatase inhibitor letrozole led to any pharmacokinetic or pharmacodynamic interaction. Twelve of 17 patients completed the core period of the trial in which 2.5 mg/day letrozole was administered alone for 6 weeks and in combination with 20 mg/day tamoxifen for the subsequent 6 weeks. Patients responding to treatment continued on the combination until progression of disease or any other reason for discontinuation. Plasma levels of letrozole were measured at the end of the 6-week period of treatment with letrozole alone and the combination and once more between 4 and 8 months on combination therapy. No further measurements were done thereafter. Hormone levels were measured at 2-week intervals throughout the core period. Marked suppression of estradiol, estrone, and estrone sulfate occurred with letrozole treatment, and this was not significantly affected by the addition of tamoxifen. However, plasma levels of letrozole were reduced by a mean 37.6% during combination therapy (P < 0.0001), and this reduction persisted after 4–8 months of combination therapy. Letrozole is the first drug to be described in the generation of E1 and E2 from androgenic precursors. The mechanism is likely to be a consequence of an induction of letrozole-metabolizing enzymes by tamoxifen and this was not further addressed in this study. It is possible that the antitumor efficacy of letrozole may be affected. Thus, sequential therapy may be preferable with these two drugs. It is not known whether tamoxifen interacts with other members of this class of drugs or with other drugs in combination.

INTRODUCTION

Estrogen deprivation is the primary mechanism of action of hormonal therapies in breast cancer. There are two main ways in which this may be achieved. The most frequent approach is to use an antiestrogen such as tamoxifen to antagonize estrogens at the estrogen receptor. An alternative is to reduce the synthesis of estrogens. In postmenopausal women, this is achieved by inhibition of the aromatase enzyme system, which is responsible for the generation of E1 and E2 from androgenic precursors.

Letrozole (CGS 20267) is a highly potent and specific nonsteroidal inhibitor of the aromatase enzyme system (1). Previous studies have demonstrated that letrozole in single oral doses ranging from 0.1–2.5 mg/day produces significant decreases in circulating E2 and E1 concentrations (2). The efficacy of aromatase inhibition has been found to be greater than 98% at the 0.5 mg/day dose and >99% at the 2.5 mg/day dose (1). A pivotal Phase IIIB/III comparative study of 0.5 mg/day letrozole versus 2.5 mg/day letrozole versus 160 mg/day megestrol acetate found that the higher dose of letrozole produced a significantly higher objective response rate (24%) compared with megestrol acetate (16%) or 0.5 mg/day letrozole (13%; Ref. 3). Time to progression and time to treatment failure were also better at the 2.5 mg/day dose of letrozole than with megestrol acetate or 0.5 mg/day letrozole. This higher dose of letrozole was also found to achieve greater efficacy than the 0.5 mg dose in another Phase IIb/III study (4): there was a significant dose effect on overall survival in favor of 2.5 mg letrozole compared with 0.5 mg letrozole. The improved tolerability of letrozole and other aromatase inhibitors compared with megestrol acetate and AG³ (3, 4) has now led to them being the first choice endocrine therapy after tamoxifen for most patients. Their efficacy and excellent tolerability have also led to their incorporation into large-scale first-line and adjuvant trials versus tamoxifen in early breast cancer.

The differences in the mechanism of action between aromatase inhibitors and tamoxifen and observations that some patients who are resistant to tamoxifen respond to an aromatase inhibitor (5, 6) have led to a series of clinical trials combining the two agents. Until now, these trials have all used AG as the aromatase inhibitor (6–8).

¹ The abbreviations used are: AG, aminoglutethimide; SHBG, sex hormone-binding globulin; LH, luteinizing hormone; FSH, follicle-stimulating hormone; AUC, ; CV, coefficient of variation; CI, confidence interval; E₁, estrone; E₂, 17β-estradiol; E₁S, estrone sulfate; CYP, cytochrome P-450.
It is generally accepted that the studies combining the aromatase inhibitor AG and tamoxifen have not led to major gains in patient benefit (6–8). A possible explanation of the apparent lack of additive benefit may be the enhancement of tamoxifen clearance, which has been found to occur in the presence of AG and results in plasma tamoxifen levels of about only 30% of those in patients treated with tamoxifen alone (9). Animal studies of a combination of aromatase inhibitor and tamoxifen are also mixed in their findings. Some indicate improved efficacy over single-agent treatment (10), whereas others show a marked benefit for the single agent (11). Thus consideration has been given to whether the combination of letrozole and tamoxifen might improve the status of patients with advanced breast cancer and their time to progression.

Because it was not known whether these two drugs would interact, a two-center, open-label, nonrandomized, within-patient comparison of the pharmacokinetics and endocrine interactions of letrozole and tamoxifen was conducted in postmenopausal women with advanced breast cancer who could benefit from treatment with aromatase inhibitors and/or tamoxifen. The primary objective was to investigate whether cotreatment of patients who had already been on letrozole treatment for 6 weeks with 6 weeks of tamoxifen influenced the pharmacokinetic profile of letrozole. The secondary objectives were as follows: (a) to assess the safety and tolerability of the treatment combination of letrozole and tamoxifen; (b) to evaluate the effects on serum hormone levels (E1, E2, E1S, SHBG, LH, and FSH); and (c) to evaluate patients for response and time to disease progression.

A separate study has been conducted to investigate whether letrozole influenced the pharmacokinetic profile of tamoxifen (12).

PATIENTS AND METHODS

Sample Size

Previous trials with letrozole (data on file; Novartis) indicated that the within-patient CV of AUC should not exceed 18%. Based on this CV, a sample size of 12 patients with completed pharmacokinetic profiles was calculated, which would provide an approximately 80% probability that the 90% CI for the ratio of AUC(letrozole/tamoxifen) to AUC(letrozole) would be contained within the equivalence limits of 0.8 and 1.25 if the two treatments were identical, i.e., if the addition of tamoxifen did not affect the AUC(letrozole).

Trial Population and Previous Treatments

The trial population consisted of postmenopausal patients with locally advanced or locoregional recurrent or metastatic breast cancer who were eligible for treatment with endocrine therapy. Patients had to have a WHO performance status of grade 0–2 and a life expectancy of at least 3 months and must have provided written informed consent to the specific protocol. All patients had documented evaluable or measurable disease with objective evidence of disease progression. Patients with estrogen receptor-negative status and patients with conditions that would prohibit proper follow-up were excluded from the trial. Previous treatment with any of the following agents was not allowed: (a) antiestrogen therapy within the last 6 months; (b) aromatase inhibitors; (c) other hormonal agents (e.g., medroxyprogesterone acetate, megestrol acetate) within the last 4 weeks; and (d) bisphosphate therapy within 6 months of starting trial treatment, if bone metastases were the sole manifestation of advanced disease.

The core treatment ran for 12 weeks. Patients received 2.5 mg letrozole daily for the first 6 weeks and continued to receive a combination of letrozole (2.5 mg) and tamoxifen (20 mg) tablets once daily until progression or any other reason for withdrawal. Patients who failed to complete the core trial were replaced.

Blood Sampling and Analytical Methods

Samples were collected into EDTA-containing tubes on week 6 and week 12 for pharmacokinetics at time 0 (i.e., just before taking the daily dose of letrozole) and at 1, 2, 4, 6, 8, and 24 h thereafter. Plasma was stored at −20°C until analysis. Plasma concentrations of letrozole were determined using a high-performance liquid chromatography method with CPG 47645 as the internal standard (13). The limit of quantification was 1.4 nmol/liter. Preliminary results from 10 patients indicated a pharmacokinetic interaction between the drugs, and for those patients still on trial, another PK sampling was done between 4 and 8 months on combination treatment to confirm whether the interaction persisted over time.

Steady-state AUC values during a dosing interval were calculated by the linear trapezoidal rule. All available samples were analyzed for letrozole concentration. AUC data of all patients with at least one complete pharmacokinetic profile were subjected to statistical analyses.

Blood for hormone analyses was collected into plain tubes before starting therapy and on weeks 2, 4, 6, 8, 10, and 12. Serum was stored at −20°C until analysis. Serum E2 and E1 levels were measured according to previously described methodology with assays having sensitivity limits of 3 and 10 pmol/liter, respectively (14, 15). E1S was measured after an initial extraction of unconjugated (free) E1 and hydrolysis of E1S to free E1. E2 was then measured after ether extraction and column chromatography on Lipidex 5000 using a solvent system of chloroform:hexane:methanol (50:50:1). [3H]E1S was added as a recovery control. The RIA was performed using the Diagnostic Services Laboratory kit (DSL-8700). The overall assay sensitivity was 10 pmol/liter. SHBG was measured using the Farmos immunoradiometric assay kit, which has a detection limit of 0.5 nmol/liter and intra- and interassay CVs of 3.2% and 8.3%, respectively. LH and FSH were measured by Abbott AxSYM. All samples from the same patient were included in the same assay batch.

Clinical Tumor Evaluation

Antitumor activity was evaluated according to the UICC criteria (16) at baseline and every 3 months thereafter or when the patient discontinued treatment. Blastic and mixed bone lesions were evaluated for progression but not for response. Performance status (WHO scale) was recorded at baseline, 6 weeks, 3 months, and every 3 months thereafter, and adverse experiences were recorded at 2-week intervals for the first 12 weeks and every 3 months thereafter.
Statistical Methodology

Pharmacokinetics. A possible effect of tamoxifen coadministration on letrozole levels was evaluated using bioequivalence testing on log-transformed AUC values, i.e., equivalence was accepted if the 90% CIs of the difference in logAUCs between two treatments were contained within the limits 0.8 and 1.25. A general linear model with a treatment effect and a patient effect was fitted to the log-transformed AUC values. First, an equivalence test was performed on the AUC values of the two combination periods (12 weeks versus >4 months of combination therapy). Next, provided the two combination periods were equivalent, equivalence was tested on the difference in logAUCs of letrozole alone versus the average of the two combination treatment periods.

Hormones. Estrogen suppression was described over time using summary statistics, geometric mean, and minimum and maximum on the log (natural base)-transformed values. For statistical purposes, when estrogen levels were below the detection limit of the assay, they were ascribed the value of the respective detection limit. In addition, SHBG, LH, and FSH were described over time using the mean, SD, quartiles, minimum, and maximum. The effect of cotreatment with tamoxifen on the hormone effects of letrozole was assessed with descriptive statistics.

RESULTS

A total of 17 patients were recruited to the trial. Two patients withdrew during monotherapy treatment and an additional 2 patients discontinued treatment at the 6 week visit. Thus, 13 patients continued into the combination treatment phase, and 12 patients completed at least 6 weeks of combination therapy. All patients were postmenopausal and had receptor-positive tumors. Their median age was 64.1 years (range, 44–88 years), and 94.1% of patients had a WHO status of 0–1.

Antitumor Efficacy. After 3 months of core treatment (6 weeks of letrozole monotherapy followed by 6 weeks of the combination treatment), 3 of 17 patients had a partial response, 9 patients remained stable, 3 patients progressed, and 2 patients were not assessable. Six months after starting study, 2 additional patients [5 of 17 patients in total; 29.4% (95% CI, 10.3–56.0%)] had achieved partial response.

Adverse Experiences. During the 6 weeks of monotherapy, 2 of 17 patients reported at least one serious adverse event, and 1 patient discontinued treatment due to an adverse event. The discontinued patient experienced a non-drug-related hematemesis after a single dose of study medication, whereas the other patient experienced a non-drug-related erythematous rash after 13 days of trial treatment. During the rest of the core trial and the follow-up period of the combination, one patient suffered from continuous hypochondrial pain that was reported as a non-drug-related serious adverse event. Another patient was discontinued on combination treatment as a result of depression and headache, which resolved after combination treatment was stopped. Adverse events reported during either phase were mainly mild to moderate in severity. The most commonly reported individual adverse events during both treatment phases, irrespective of trial drug relationship, were depression, fatigue, nausea, hot flushes, and abdominal pain. Weight increases (5.9% versus 30.8%) and coughing (5.9% versus 30.8%) were reported by more patients during combined therapy than during monotherapy. With these exceptions, and taking into account the small patient numbers, the pattern of adverse events and their frequency of reporting were similar during both treatment phases. It should also be noted that the combination treatment period extended over a longer time period, increasing the likelihood that more events would occur in the combination phase than in the limited 6-week time period of monotherapy.

The study drug-related adverse events are listed by body system for those reported in ≥10% of patients in either treatment period in Table 1. The most commonly reported study drug-related adverse events were hot flushes, fatigue, and weight gain. Weight gain was most discrepant in both treatment phases and was observed in 4 of 13 patients during combined treatment and 1 of 17 patients during monotherapy. All of the most commonly reported (≥10%) study drug-related adverse reactions were known to be associated with letrozole or tamoxifen. Coadministration of the two drugs did not result in an increased incidence of any event, with the possible exception of weight gain. However, even in this case, the numbers are too low for definitive comment. At baseline, all patients had a WHO performance status grade between 0 and 2, with the majority of patients having a WHO performance status of grade 1. This situation was essentially unchanged through the whole 12 weeks of the study, although one patient had deteriorated to grade 3 at 12 weeks. There were no changes of concern in the hematological and blood chemistry analyses during either of the study periods.

Pharmacokinetics. In all but one patient, letrozole plasma concentrations were lower when letrozole was given together with tamoxifen (Table 2). The levels after 4–8 months of combination therapy were, in general, similar to those after 6 weeks of combination treatment. Fig. 1 displays the mean letrozole plasma levels for the three treatment periods. The mean AUCs are shown in Fig. 2. The AUC values between 4 and 8 months on combination therapy were not significantly different from those after 6 weeks of combination treatment (90% CI, 44–88 years), and 94.1% of patients had a WHO status of 0–1.

<table>
<thead>
<tr>
<th>Body system</th>
<th>Letrozole (n = 17)</th>
<th>Letrozole plus tamoxifen (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with adverse events</td>
<td>13 (76.5)</td>
<td>13 (100.0)</td>
</tr>
<tr>
<td>Body as a whole</td>
<td>3 (17.6)</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (11.8)</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>Weight increase</td>
<td>1 (5.9)</td>
<td>4 (30.8)</td>
</tr>
<tr>
<td>Digestive system</td>
<td>5 (29.4)</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2 (11.8)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>3 (17.6)</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>Depression</td>
<td>2 (11.8)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Skin and appendages</td>
<td>7 (41.2)</td>
<td>7 (53.8)</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>3 (17.6)</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (5.9)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Special senses</td>
<td>2 (11.8)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Urogenital and reproductive system</td>
<td>1 (5.9)</td>
<td>4 (30.8)</td>
</tr>
<tr>
<td>Vaginal spotting</td>
<td>1 (5.9)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>0</td>
<td>2 (15.4)</td>
</tr>
</tbody>
</table>
However, AUC values of letrozole treatment alone were significantly higher than those of the combination treatment: the ratio of AUC (letrozole alone) to AUC (combination) was 1.60 with a 90% CI of 1.46–1.76 (P, 0.0001), which corresponds to a mean AUC reduction of 37.6% in the combination periods.

**Pharmacodynamics.** The suppression of serum estrogen levels and effects on SHBG, LH, and FSH compared to baseline are summarized in Table 3. Twelve patients had at least one endocrine measurement available and are included in the analysis. \( E_1 \), \( E_2 \), and \( E_1S \) levels dropped significantly after baseline, with many values below the detection limits of the respective assays. The mean estrogen levels underestimated the suppressive effects of letrozole because undetectable values were given the value of the assay detection limit for statistical purposes. No significant changes were seen after tamoxifen was added at 6 weeks. SHBG, LH, and FSH did not change significantly from baseline during either phase. A slight decrease in LH and FSH levels and an increase in SHBG levels were seen when tamoxifen was added at 6 weeks; however, the sample size was too low to detect a significant difference.

**DISCUSSION**

This study was conducted largely to ensure that there were no unexpected pharmacokinetic or pharmacological interactions between letrozole and tamoxifen that would preclude their combination in future clinical studies. It has previously been noted that the aromatase inhibitor AG enhanced the clearance of tamoxifen in advanced breast cancer patients (9). AG shows similar interaction with a number of other drugs and is dependent on the induction of CYPs. In contrast, a recent study has reported that letrozole has no impact on the plasma levels of tamoxifen or its major metabolites (12).

The impact of tamoxifen in reducing the plasma AUC of letrozole by 38% on average was unexpected. Despite the very widespread use of tamoxifen over a 20-year period and its application in patient groups that are frequently taking many drugs, no such interaction has been reported previously. It is not known whether tamoxifen interacts with other triazole aromatase inhibitors, e.g., anastrozole, in this way. The extension of this study beyond the core 12 weeks allowed a second profile to be made on combination therapy and showed that this change in pharmacokinetics was not transient, nor did it increase in magnitude during continued therapy. The reduction varied between patients, ranging from no reduction in one patient to a reduction of almost 70%.

The decreased drug levels are estimated to correspond to a daily dose of approximately 1.5–2 mg of letrozole if letrozole were administered alone. The clinical consequences of this interaction have not been studied. The patients still received tamoxifen as standard therapy, and, as discussed above, data from another trial indicate that tamoxifen levels were not affected by letrozole (12). The response rate and durability of

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**Table 2** Letrozole AUC values (h.nmol/liter) for individual patients after 6 weeks monotherapy (letrozole, LET), and 6 weeks and >4 months combination therapy (letrozole + tamoxifen, LET + TAM)

<table>
<thead>
<tr>
<th>Patient</th>
<th>LET (6 weeks)</th>
<th>LET + TAM (6 weeks)</th>
<th>LET + TAM (&gt;4 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7570</td>
<td>4600</td>
<td>4980</td>
</tr>
<tr>
<td>2</td>
<td>4360</td>
<td>4590</td>
<td>4770</td>
</tr>
<tr>
<td>3</td>
<td>7880</td>
<td>6430</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6310</td>
<td>4370</td>
<td>4110</td>
</tr>
<tr>
<td>5</td>
<td>14700</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>6</td>
<td>16400</td>
<td>6660</td>
<td>6500</td>
</tr>
<tr>
<td>7</td>
<td>8310</td>
<td>5210</td>
<td>6420</td>
</tr>
<tr>
<td>8</td>
<td>5840</td>
<td>3380</td>
<td>3048</td>
</tr>
<tr>
<td>9</td>
<td>11300</td>
<td>9840</td>
<td>9190</td>
</tr>
<tr>
<td>10</td>
<td>13300</td>
<td>5470</td>
<td>4040</td>
</tr>
<tr>
<td>11</td>
<td>11600</td>
<td>5670</td>
<td>5580</td>
</tr>
<tr>
<td>12</td>
<td>9570</td>
<td>6040</td>
<td>6590</td>
</tr>
<tr>
<td>13</td>
<td>10100</td>
<td>6630</td>
<td>7270</td>
</tr>
<tr>
<td>14</td>
<td>4090</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Mean</td>
<td>9381</td>
<td>5741</td>
<td>5682</td>
</tr>
<tr>
<td>SD</td>
<td>3761</td>
<td>1636</td>
<td>1741</td>
</tr>
<tr>
<td>n</td>
<td>14</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

* Patient withdrew from the study before the profile being taken.

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**Fig. 2** Comparison of the mean ± SD AUC for plasma letrozole after 6 weeks of treatment with letrozole alone, 6 weeks of treatment with letrozole plus tamoxifen, and >4 months of treatment with letrozole plus tamoxifen. The ratio of AUC (letrozole alone):AUC (combination, 6 weeks) was 1.60 (P < 0.0001).
responses in this trial are similar to those observed previously for patients treated with letrozole alone (3, 4), but the small numbers of patients in this study preclude a reliable estimate of antitumor efficacy. In two large Phase Ib/III trials, the dose of 2.5 mg/day letrozole appeared to achieve a longer time to tumor progression than the 0.5 mg/day dose and was superior in terms of survival (3, 4). Thus, the reduced letrozole levels with the combination may not provide the full additive benefit. Unless additional studies demonstrate a clear benefit for the combination aromatase inhibitor/tamoxifen over sequential use of the drugs, sequential application would seem to be preferable for letrozole for letrozole and tamoxifen.

The reason for the reduction in letrozole levels may lie in an alteration of the absorption of letrozole or in a change of its clearance during tamoxifen treatment. The first hypothesis appears to be unlikely because there are no indications in the literature that tamoxifen alters the absorption behavior of other drugs. In addition, letrozole is reasonably soluble, particularly at low pH values, and is rapidly and completely absorbed after oral dosing (17).

Changes in the clearance of letrozole by tamoxifen may be due to a protein binding interaction or an interaction at the level of the enzymes involved in the metabolism of letrozole. Both compounds bind mainly to albumin. However, in vitro experiments on selected plasma samples from this study did not show an altered plasma binding of letrozole in the combination periods compared to the treatment with letrozole alone (18). Thus, protein displacement as a cause for the reduction of letrozole levels appears to be very unlikely.

Tamoxifen and letrozole use a common CYP isoenzyme in their major metabolic elimination pathways. Formation of the main metabolite of letrozole is catalyzed by CYP3A4 and CYP2A6 (19). The contribution of each individual isoenzyme to this pathway is not known. The main metabolic transformation of tamoxifen to N-desmethyltamoxifen is mediated by CYP3A4 and probably also by CYP2C (20, 21). In animal experiments, tamoxifen has been shown to induce the rat isoenzymes CYP2B1 and CYP3A1 (22, 23) and to increase 6β- and 16α-hydroxylation of testosterone in the rat (22). This indicates that enzymes homologous to the human CYP3A family are induced by tamoxifen. A case report in a single patient describes a decrease in the plasma levels of doxepin (a tricyclic antidepressant) during tamoxifen coadministration that may be due to CYP enzyme induction (24). However, apart from this report, tamoxifen has not been described as a CYP inducer in the clinical literature, but it is important to note that systematic studies on drug-drug interactions have apparently not been performed (24).

Despite this rather sparse support from the literature, the hypothesis of an induction of letrozole-metabolizing enzymes (possibly CYP3A4) by tamoxifen remains the most likely one.

Hormone levels (E1, E2, and E1S) dropped significantly as compared to baseline during letrozole monotherapy. The addition of tamoxifen did not cause any significant change to the diminished hormone levels. This suggests that although letrozole levels were reduced by the addition of tamoxifen, the effect of letrozole on hormone levels remains largely unaltered. Any minor alterations are unlikely to be detected because many estrogen levels were below the limit of detection of the assay. Levels of SHBG, LH, and FSH did not change significantly from baseline on the addition of letrozole, as has been reported previously (2). The apparent decreases in LH and FSH levels and increases in SHBG levels on the introduction of tamoxifen are also consistent with previous reports on tamoxifen alone (25). Thus, the pharmacodynamic changes with the two drugs appear to be independent of one another and would not be expected to compromise their activity.

Overall, the addition of tamoxifen did not increase the incidence of adverse events, with the possible exception of weight gain. All side effects recorded had previously been reported with letrozole or tamoxifen individually.

These data on reduced letrozole levels may have significant implications beyond the immediate combined usage of these two drugs. The widespread usage of tamoxifen inevitably results in its combined application with a large number of other drugs. The lack of clinical reports of toxic interactions indicates the probable absence of any safety concerns, but it is possible that tamoxifen may unexpectedly interact with other drugs and that these interactions might affect the efficacy of the drugs, particularly in cases where there is a steep dose-response curve.

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