

An electronic non-interventional pharmacovigilance study of early-stage breast cancer patients on adjuvant treatment with anastrozole (Arimidex®)

Anastrozol (Arimidex®) adjuvant tedavi alan erken dönem göğüs kanseri hastalarında elektronik müdahalesiz farmakovijilans çalışması

Necdet USKENT,¹ Atilla ÇÖKMEZ,² Murat Kemal ATAHAN,² Erol AKSAZ,³ Nilüfer GÜLER,⁴ Mahmut MÜSLÜMANOĞLU,⁵ Vahit ÖZMEN⁵

¹Department of Medical/Hematologic Oncology Anadolu Medical Center, Kocaeli;

²1st Department of General Surgery, Izmir Atatürk Training and Research Hospital, Izmir;

³Department of General Surgery, Ali Osman Sonmez Oncology Hospital, Bursa;

⁴Department of Medical Oncology, Hacettepe University Faculty of Medicine, Ankara;

⁵Department of General Surgery, Istanbul University, Istanbul Faculty of Medicine, Istanbul, all in Turkey

OBJECTIVES

To identify adverse events profile of patients with breast cancer in Turkey during use of anastrozole.

METHODS

Between 2001-2006, 874 postmenopausal women with early-stage breast-cancer treated with anastrozole (1 mg/day) were included. We used electronic case report forms at 3rd, 6th, 12th, 18th and 24th months after the 1st visit.

RESULTS

Mean age of the patients was 60.2±9.6 years. Mean follow-up period was 11.7±7.5 months. Anastrozole was discontinued in 17 (1.9%) patients due to cancer recurrence during observation period. Thirty-five adverse events (16-mild, 3-moderate, 16-severe) were identified in 18 patients. In 4 patients treatment was discontinued. Of the patients attending follow-up visits %90 experienced no difficulties in taking treatment as prescribed, and 82% and 88% took treatment exactly as prescribed in 6th and 7th visits, respectively.

CONCLUSION

Compliance and drug tolerability assessments revealed that Anastrozole was well tolerated in 83.2% of the patients, and treatment compliance was high in 81.7% of the patients.

Key words: Anastrozole; early breast cancer; safety.

AMAÇ

Türkiye'deki hastalarda anastrozolün klinik kullanımı sırasında gelişen yan etki profili bilgilerinin tanımlanması amaçlandı.

GEREÇ VE YÖNTEM

Çalışmaya 2001-2006 yılları arasında erken dönem meme kanseri tanısı konan ve anastrozol (1 mg/gün) tedavisi alan toplam 874 postmenopozal hasta dahil edildi. İlk viziten sonra 3., 6., 12., 18. ve 24. aylarda elektronik olgu rapor formları kullanıldı.

BULGULAR

Hastaların yaş ortalaması 60.2±9.6 yıl, ortalama izlem süresi 11.7±7.5 aydı. On yedi (%1.9) hastada izlem sırasında hastalık nüks ettiğinden anastrozol tedavisi sonlandırılarak başka tedavilere geçildi. On sekiz hastada görülen 35 yan etkinin, 16'sı hafif, 3'ü orta, 16'sı ise şiddetli idi. Dört hastada tedavi sonlandırıldı. Kontrollere gelen hastaların yaklaşık %90'ı ilacı tarif edildiği şekilde almakta zorluk çekmediklerini, hastaların %82'si 6. vizitte ve %88'i de 7. vizitte ilacı tam anlamıyla tarif edildiği şekilde aldıklarını bildirmiştir.

SONUÇ

Tedaviye uyum ve ilaç toleransı değerlendirme sonuçlarına göre, anastrozolün hastaların %83.2'sinde oldukça iyi tolere edildiği ve hastaların %81.7'sinde tedaviye uyumun yüksek olduğu bulunmuştur.

Anahtar sözcükler: Anastrozol; meme kanseri; güvenilirlik.

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Correspondence (İletişim): Necdet USKENT, M.D. Anadolu Medical Center, Department of Medical-Hematologic Oncology, Kocaeli, Turkey.
Tel: +90 - 444 42 76 e-mail (e-posta): necdet.uskent@anadolusaglik.org

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Breast cancer accounts for 24% of female cancers and 14% of cancer related deaths. Adjuvant systemic therapy improves overall and disease-free survival.^[1,2] In developed countries, breast cancers are encountered mostly in postmenopausal women (50-75%)^[3] and almost two thirds of these cancers are hormone-receptor positive.^[4] Hormone sensitive breast cancers grow under the effect of estrogen and great advances have recently been seen with new hormonal agents for adjuvant therapy. Until recently, the standard treatment of hormone sensitive breast cancers during the postmenopausal period was tamoxifen.^[5,6] Tamoxifen shows its effect by blocking estrogen receptors on target cells and prevents new hormone positive breast cancers. However, there is a partial agonist effect that confers demonstrable estrogenic activity in the form of increased risk of side effects, such as vaginal bleeding and endometrial cancer. The partial agonist effects have already been shown with the protective effects on bone mineral density associated with tamoxifen and raloxifen intake. An alternative hormonal therapy for menopausal patients is selective aromatase inhibitors. Adrenal androgens are the main source of estrogens in postmenopausal women; therefore, aromatase inhibitors have an important place in the treatment of hormone sensitive breast cancers.^[7] Aromatase inhibitors prevent the conversion of adrenal androgens to estrogen in peripheral tissues (muscles, adipose tissues, etc). Aminoglutethimide and formestane were the first aromatase inhibitors developed for the treatment of advanced stage breast cancers and became the treatment of choice of patients non-responsive to tamoxifen.^[7] However, these early aromatase inhibitors had high risk of unwanted side effects because of their effects on steroid biosynthesis, apart from estrogen biosynthesis. Anastrozole, a third generation selective aromatase inhibitor, has proven to be better tolerated than aminoglutethimide, formestane and megestrol.^[7,8] Anastrozole (Arimidex[®]) has been found to be more effective than tamoxifen in the adjuvant treatment of early-stage breast cancer and has fewer side effects.^[5,6,8] Anastrozole markedly reduces serum estradiol concentrations.^[9,10] Anastrozole is licensed and used in many countries, including Turkey.^[11] However,

there was no study concerning the assessment of side effects of Anastrozole in our country.

This study was a national, open-label, multi-center, non-comparative, non-interventional, observational pharmacovigilance study. Data were collected electronically.

Pharmacovigilance studies consist of identifying side effects, which have previously been overlooked during daily treatment, investigating possible changes in previously identified side effects, identifying approaches to develop drug safety, gathering additional information associated with optimization of drug use, and evaluating effects of the interventions.

The aim of this study was to evaluate safety and patient compliance and identify the prevalence of drug-related adverse events (AE) in Turkey in patients with early-stage breast cancer who were treated with anastrozole.

MATERIALS AND METHODS

This study was conducted at 75 centers that were treating and following up patients diagnosed with breast cancer between 2001 and 2006. Postmenopausal patients with histological diagnosis of early stage breast cancer (Stage I, II) were included in the study. After primary surgical therapy and/or adjuvant chemotherapy, adjuvant hormonal therapy with anastrozole (Arimidex[®]) was started in hormone receptor(s) positive patients. Exclusion criteria were presence of distant metastasis; abnormal renal and liver function tests; prior hormonal agent for prevention of breast cancer or adjuvant therapy; history of malignancy involving the other systems (apart from treated basal cell carcinoma or in situ cervical cancer); and severe systemic disease. All participants provided written informed consent.

All patients received the treatment dose (1 mg/day) of anastrozole. Electronic case report forms (uploaded on laptops given to participating centers) were used to increase the quality of collected data. The electronic case report forms (eCRFs) facilitated registration of data by physicians; the electronic records also reduced errors in recording

information and increased the reliability of data. During the study, the treatment pattern of physicians to the patients was not interfered; only the data regarding adverse events, the patient compliance and satisfaction were collected.

After the first visits of the patients, patients were followed up at 3rd, 6th, 12th, 18th and 24th month and if the physician requested, an additional last visit was performed. During every visit, patient compliance with treatment was evaluated and adverse events were recorded.

To evaluate the patient compliance, four questions asked to the patients: I) When did the patient begin to use the drug?, II) How has the patient been using the drug?, III) Did the patient have difficulty in using the drug?, and IV) Has the patient ever forgotten to use the drug?.

In every visit, after recording the symptom evaluation part of the eCRF for each patient, patient reported AEs were also filled by the physician. An adverse event was considered to be drug related when fulfilled at least one of the following criteria: a) if there is a logical time lapse and sequence between the administration of the drug and the development of AE, b) if the known clinical condition of the patient cannot be logically explained by environmental and toxic factors or the other treatments applied to the patient, c) if AE disappears or decrease when drug is ceased (in the exceptional situations, like bone marrow suppression, the drug relation with AE cannot be ignored even though AE does not disappear when drug is ceased), d) if AE follows a known and likely response pattern for the suspected drug, e) if AE is appeared, when the drug is re-administered.

RESULTS

A total of 874 patients were included in the study. The mean age of the patients was 60.2±9.6 years, and the mean follow-up period was 11.7±7.5 months (median= 12 months).

Anastrozole treatment was terminated in 17 (1.9%) patients following identification of recurrence during the follow-up period. A total of 35 patient-reported AEs were recorded in 18 patients.

Table 1

Number of AEs according to the visits

	Number of patients n	Number of adverse events n (%)
Visit 2	432	5 (1.2)
Visit 3	334	6 (1.8)
Visit 4	238	4 (1.7)
Visit 5	146	2 (1.4)
Visit 6	73	1 (1.4)
Visit 7	6	0 (0.0)

The number of AEs during each visit was shown in Table 1. The AEs were joint and muscle pain (n=9, 1.0%), hot flushes (n=5, 0.6%), vaginal dryness (n=4, 0.5%), weight gain (n=3, 0.3%), somnolence (n=3, 0.3%), vaginal bleeding (n=2, 0.2%), nausea (n=2, 0.2%), skin eruptions (n=2, 0.2%), asthenia (n=2, 0.2%), dyspnea-cough (n=1, 0.1%), cholelithiasis (n=1, 0.1%), and hair loss (n=1, 0.1%) (Table 2). The physicians considered 5 AEs as drug related for 5 patients, 3 AEs as possibly drug related for 2 patients, and 3 AEs as non-drug related for 2 patients; however, the causality relationship between AEs and the used drug could not be assessed in 9 patients. Joint and muscle pain and hot flushes were definitely associated with the drug, whereas, the association of cholelithiasis, vaginal dryness,

Table 2

Distribution of adverse events

Adverse event	n	%
Joint and muscle pain	9	1.0
Hot flushes	5	0.6
Vaginal dryness	4	0.5
Weight gain	3	0.3
Somnolence	3	0.3
Vaginal bleeding	2	0.2
Nausea	2	0.2
Skin eruptions	2	0.2
Asthenia	2	0.2
Dyspnea-cough	1	0.1
Cholelithiasis	1	0.1
Hair loss	1	0.1

and vaginal bleeding with the drug was uncertain. Of 35 AEs, 16 were described as mild, 3 as moderate, and 16 as severe; however, two of them were serious AEs. In addition, no death occurred due to AE. Four patients (3 patients with severe AE and 1 with moderate AE) showed improvement of muscle and joint pain when the drug use was stopped. Symptoms were observed again only in one patient with muscle and joint pain when the drug was re-administered.

Approximately 90% of the patients who attended the follow-up visits reported that they experienced no difficulties in taking the drug, while 82% and 88% of the patients reported that they took the treatment exactly as prescribed in 6th and 7th visits, respectively. At the end of the last visit, the physicians were questioned about the compliance of the patients. Treatment compliance was evaluated in 126 patients and was found to be very good in 50% (n=63), good in 32% (n=40), moderate in 9% (n=12), and weak in 9% (n=11) of patients, respectively. The drug tolerability was very high in 49% (n=61), high in 34% (n=43), moderate in 10% (n=12), and low in 7% (n=9) of patients, respectively. Joint and muscle pain, and hot flushes were evaluated by the investigator as being causally related to treatment; whereas, the association of cholelithiasis, vaginal dryness, and vaginal bleeding with the drug was reported to be doubtful.

DISCUSSION

Aromatase inhibitors play an important role in the treatment of hormone sensitive early-stage breast cancers in postmenopausal women. Extensive studies have reported that new-generation aromatase inhibitors such as anastrozole, letrozole and exemestane are good treatment option for hormonal therapy. They are more effective than tamoxifen regarding decreasing local and systemic recurrence and increasing survival rates. They also have less side effects than tamoxifen.^[12-15] In the present study, 35 adverse events were observed in 18 patients out of 874 patients during the follow-up period (the mean follow-up duration, 11.7±7.5 months). Of these adverse events, 54.3% were mild and moderate.

Side effects reported in association with anastrozole therapy include gastrointestinal system disorders, headache, asthenia, hot flushes, bone pain, back pain, dyspnea, peripheral edema, thromboembolic events, and gynecological complications. Comparative studies versus tamoxifen have demonstrated fewer side effects in patients receiving Anastrozole, the side effects have been at a level that has been well tolerated.^[4,8,14-17] In the present study, no adverse event related mortality was observed; the most frequent adverse events were joint and muscle pain, and gynecological complications. The ratio of patients with high and very high drug tolerability was found to be greater than 80%.

The ATAC (arimidex, tamoxifen, alone or in combination) study group has compared anastrozole with tamoxifen over a follow-up period of approximately 100 months. The recurrence rate, including distant recurrence, is significantly lower in the Anastrozole group than the tamoxifen group and this effect continues beyond completion of the 5-year treatment period.^[4] Serious, life-threatening adverse events such as occurrences of thromboembolism, ischaemic cerebrovascular events, and endometrial cancer were observed to be fewer in anastrozole treatment than tamoxifen. No difference was observed between the anastrozole and tamoxifen groups in cardiovascular morbidity and mortality.^[4] In our study, no cardiovascular or cerebrovascular events were observed.

The fracture rate was higher in the anastrozole group; however, there was no difference between the groups at the end of the 5-year active treatment period.^[4] In two studies on anastrozole, while loss of bone mineral density was observed among common side effects of anastrozole,^[24] renal failure associated with sclerosing glomerulonephritis was rarely encountered.^[25] In a study by Brufsky, it has been reported that the treatment for 1-5 years may lead to nearly 7.2% loss of bone mineral density.^[24] Women in the substudy of ATAC receiving anastrozole for 5 years lost a median of 6.08% of bone mineral density from the lumbar spine and 7.24% from the hip. The spinal bone loss was faster during the first 2 years, whereas loss from the hip occurred at a steady rate.^[26] The most frequent ad-

verse event in our study was joint and muscle pain, as well as no fracture event was reported. When compared with other endocrine agents, anastrozole leads to less weight gain than megestrol acetate; it does not have the partial agonistic activity on estrogen receptors that tamoxifen has; and does not lead to endometrial proliferation.^[9,22]

Complaints of arthralgia have been reported in approximately 25% of females receiving anastrozole treatment. Since arthralgia is also associated with tamoxifen use, it is difficult to determine which complaints are associated with aromatase inhibitor therapy and which are associated with postmenopausal status.^[23] In the present study, joint and muscle pain complaints rate was very low (1%). This might be attributed to the fact that patients did not report adverse events because of the fear of termination of treatment, considering the events as unimportant, or ignoring the events as they were pre-exist (for instance patient with arthritis did not report arthralgia as adverse event). Additionally, the physicians might insufficiently question the adverse events of patients. The drop-out of patients in the follow up visits might also be another factor affecting the low rate of complaints.

In the compliance studies conducted with anastrozole, the compliance rate was between 62% and 88%, depending on the follow-up period.^[27] In the present study, the ratio of patients with high and very high treatment compliance was found to be greater than 80%.

CONCLUSIONS

The types of AEs related to medication in our study are consistent with the literature. Anastrozole was well tolerated in 83.2% of the patients, and compliance with treatment was high in 81.7% of the patients. The relatively low prevalence of reported AEs is due to the observational nature of the study. The findings demonstrated that anastrozole has a high tolerability profile in patients with hormone receptor positive breast cancer in Turkey. These results are consistent with other findings in the literature.

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