COMPLiance and Arthralgia in Clinical Therapy: the COMPACT trial, assessing the incidence of arthralgia, and compliance within the first year of adjuvant anastrozole therapy


1Department of Gynecology, Endocrinology and Oncology, Philipps University of Marburg, Marburg; 2Department of Obstetrics and Gynecology, Klinikum Offenbach, Offenbach; 3Department of Rheumatology, Klaus-Miehlke-Hospital, Wiesbaden; 4Institute for Medical Biostatistics, Epidemiology and Informatics, Johannes Gutenberg-University of Mainz, Mainz; 5Office-based Professional Association Gynecologic Oncologists e.V. in Germany (BNGO e.V.), Berlin; 6Department of Biometrics, d.s.h. Statistical Services GmbH, Rohrbach; 7Professional Association of Gynaecologists, Steinbach; 8University Women’s Hospital, Ulm; 9Outpatient Clinic for Psychotherapy, Philipps University of Marburg, Marburg; 10University Women’s Hospital, Tübingen; 11Medical Affairs, AstraZeneca GmbH, Wedel; 12Breast Center, Department OB&GYN, University of Munich, Munich, Germany

Received 31 July 2013; revised 27 September 2013; accepted 14 October 2013

Background: This prospective study evaluated the relationship between arthralgia and compliance during the first year of adjuvant anastrozole therapy in postmenopausal women with hormone receptor-positive early breast cancer.

Patients and methods: COMPliance and Arthralgia in Clinical Therapy (COMPACT) was an open-label, multicenter, noninterventional study conducted in Germany. Patients had started adjuvant anastrozole 3–6 months before the study start. The primary end points were arthralgia, compliance, and the relationship between compliance and arthralgia, assessed at specific time points.

Results: Overall, 1916 patients received upfront anastrozole. Mean arthralgia scores were increased from baseline at each visit up to 9 months. Compliance with anastrozole therapy gradually decreased over time from baseline to 9 months (P < 0.001). At 9 months, investigators estimated that >95% of patients were compliant versus patient reports of <70%. There was a significant association between arthralgia mean scores and noncompliance at 6 months (P < 0.0001), 9 months (P < 0.0001), and overall (P < 0.0001). Over time, new events or impairment of existing arthralgias were reported in 14% (3 months), 11% (6 months), and 9% (9 months) of patients.

Conclusion: Arthralgia is important in the clinical management of women with early breast cancer and may contribute to noncompliance and clinical outcomes.

ClinicalTrials.gov identifier: NCT00857012.

Key words: anastrozole, aromatase inhibitors, arthralgia, breast neoplasms, patient compliance

introduction

Third-generation aromatase inhibitors (AIs) are a well-established, cost-effective component in the adjuvant endocrine treatment of postmenopausal women with hormone receptor-positive (HR+) early breast cancer [1–3]. AI therapy requires long-term daily self-administration of an oral medication, and adherence to this regimen is essential in achieving optimal efficacy. Adherence of <80% with endocrine therapy has been shown to be associated with an increase in all-cause mortality [4]. As such, poor compliance observed with AI therapy in patients with breast cancer is a cause for concern. Furthermore, retrospective data indicate low compliance levels with endocrine therapy [5, 6], which appear to decline over time [6, 7].

Reasons for poor adherence to prescribed breast cancer treatment regimens are multiple and complex [5, 8]; however, AI-induced arthralgia is considered as one barrier to optimal adherence. Arthralgia (joint pain) is commonly experienced by women at menopause, where it is thought to result from a reduction in estrogen levels. Thus, AI-induced arthralgia is believed to be a side-effect of the estrogen deprivation associated with AI therapy [9]. In clinical trials, AIs are more often associated with arthralgia than tamoxifen [10, 11], potentially due to their different mechanisms of action.
Despite its prevalence, the cause and management of arthralgia remains an area of uncertainty among oncologists. Although guidelines exist, they are often not utilized effectively in clinical practice. Given the role of AIs in this setting, all disciplines need to be familiar with the optimal management of AI-induced arthralgia [12]. To date, no prospective data from daily routine clinical practice are available on the effects of AI-induced arthralgia on patient compliance with therapy.

Here, we present the results of COMPliance and Arthralgia in Clinical Therapy (COMPACT), a prospective study evaluating the relationship between arthralgia and compliance during the first year of AI therapy in postmenopausal women with HR+ early breast cancer.

methods

study design and patients

COMPACT was an open-label, multicenter, noninterventional study (NCT00857012) conducted in Germany between April 2009 and March 2011 under daily routine conditions. Postmenopausal women ≥18 years with histologically or cytologically confirmed HR+ early breast cancer, who had started adjuvant endocrine treatment with anastrozole, either upfront or following 2–3 years’ tamoxifen therapy (‘switch’) for at least 3 months and up to 6 months before the study start, were enrolled. Patients must have had breast cancer surgery and, if applicable, received radiation therapy and/or neo/adjuvant chemotherapy. Patients were ineligible if they received concomitant treatment known to affect sex hormone status or to interfere with tamoxifen.

Patients underwent standard routine care, and all treatment decisions were independent of the program. Patients were discontinued from the study if their breast cancer recurred, or they ceased adjuvant endocrine treatment or switched to treatment with tamoxifen or a different AI. All patients provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was obtained before study initiation.

outcomes

The primary end points were the assessment of arthralgia scores and patient compliance within the first year of anastrozole treatment, stratified by upfront and switch therapy, and assessment of the relationship between compliance and arthralgia scores.

Secondary end points included assessment of the incidence of arthralgias within the first year of anastrozole therapy, stratified by upfront and switch therapy, and assessment of safety and tolerability of anastrozole.

assessment

Previously developed support materials (letters/brochures) including information on breast cancer, coping with the diagnosis, lifestyle, and diet were mailed to all patients at specific time points throughout the study.

Patient questionnaires were sent at baseline and 3, 6, and 9 months (visits 1, 2, and 3) after study start. Data on arthralgia intensity/incidence and patient compliance with anastrozole were assessed at baseline and visits 1, 2, and 3. Arthralgia incidence was also assessed retrospectively for the 4 weeks before enrollment.

Arthralgia was assessed using the Rheumatoid Arthritis Symptom Questionnaire (RASQ). Compliance with anastrozole was assessed using documentation collected from both the doctor and the patient (via patient questionnaire) (see supplementary material for RASQ description and compliance questionnaires, available at Annals of Oncology online). Patients were defined as being compliant when both the doctor and the patient rated compliance to be ≥80% (i.e. the patient had taken ‘almost all’ or ‘all’ anastrozole tablets in the observed period).

Safety was assessed throughout the study. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA, version 11.1).

The safety population was used for the safety analysis and the intent-to-treat population for the primary analysis of arthralgia and compliance.

statistical analysis

All statistical tests were carried out two-sided at a 5% significance level using the SAS version 9.2. Analysis of association was person-based and each time point was analyzed separately. No adjustments were used for logistic regression analysis. Determination of the sample size and details of statistical analyses are provided in supplementary material, available at Annals of Oncology online.

results

patients

Between Q1 2009 and Q4 2010, 2313 patients were screened across 334 centers in Germany; 2210 evaluable patients were considered for analysis. Of these, 1916 received upfront therapy and 294 received switch therapy with anastrozole (Figure 1). After 9 months, 76.7% of patients in the upfront group were available for the follow-up. Results from the switch therapy group are not reported here because of the small patient population, limiting the ability to draw strong conclusions from any across-group comparison. However, these data are reported elsewhere [13]. Baseline patient characteristics of the upfront therapy group are summarized in Table 1.

primary end point: arthralgia

Mean arthralgia scores were increased from baseline at each visit (supplementary Figure S1, available at Annals of Oncology online). After 9 months of anastrozole therapy, mean scores were significantly increased from baseline (21 mm) by 5 mm [95% confidence interval (CI) 4–6; P < 0.05, patients with assessments at baseline and after 9 months].

primary end point: compliance

Patient compliance with anastrozole therapy gradually decreased over time from baseline to 9 months (82–66%; odds ratio 0.54; 95% CI 0.47–0.61; P < 0.001; supplementary Figure S2A, available at Annals of Oncology online). Investigators gave higher estimates of compliance with anastrozole therapy than patients throughout the study (supplementary Figure S2B, available at Annals of Oncology online). At 9 months, investigators estimated that >95% of patients were compliant versus patient reports of <70% compliance.

primary end point: relationship between compliance and arthralgia scores

Mean arthralgia scores were positively correlated with noncompliance with anastrozole from 0 to 9 months (Figure 2). There was a significant association between arthralgia mean scores and noncompliance at 6 months (P < 0.0001), 9 months (P < 0.0001), and overall (P < 0.0001). No significant association...
was observed at 3 months. At 6 months, an increase in mean scores of arthralgia by 10 mm on a 100-mm visual analog scale resulted in 1.23-fold higher odds for noncompliance with anastrozole therapy (95% CI 1.13–1.34). The odds for noncompliance were 1.28-fold higher at 9 months (95% CI 1.15–1.42) and 1.16-fold higher over the whole study period (95% CI 1.11–1.21). At 3 and 6 months, a 10-mm increase from the preceding arthralgia mean score resulted in 1.14-fold higher odds ($P = 0.0139$; 95% CI 1.03–1.27) and 1.22-fold higher odds ($P < 0.0001$; 95% CI 1.11–1.35) for noncompliance, respectively. No significant association was observed at 9 months.

**secondary end point: incidence of arthralgias**

At baseline, patients reported a higher incidence of both pre-existing and new arthralgias than investigators (supplementary Figure S3, available at *Annals of Oncology* online). Retrospective assessment of pre-existing arthralgias showed that 12% of patients experienced one or more arthralgia events before the start of anastrozole therapy. After starting therapy until enrollment, 17% of patients experienced new arthralgias. Over time, new events or impairment of existing arthralgias were reported in 14% (3 months), 11% (6 months), and 9% (9 months) of patients.

**safety**

The most frequently reported AEs were arthralgia (44%), hot flush (6%), fatigue (4%), bone pain (3%), and insomnia (2%) (Table 2). The most frequently reported AEs considered to be drug related by the investigator were arthralgia (36%), hot flush (5%), fatigue (3%), hyperhidrosis (2%), bone pain (2%), and alopecia (2%). The incidence of serious AEs (3%) and AEs that led to treatment discontinuation (5%) was low. Seven (0.4%) patients died during the study due to AEs considered to be unrelated to study drug by investigator or sponsor assessment.

**discussion**

The COMPACT study provides comprehensive data on overall compliance rates with anastrozole therapy in postmenopausal women with HR+ early breast cancer. Results showed that
patient compliance decreased and arthralgia scores increased over an observed time span of up to 9 months. These findings are consistent with results from two previous studies that revealed adherence rates to anastrozole therapy decreased each year to 62–79% at year 3 [6], and that AI-induced musculoskeletal problems worsened or incidence increased up to 2 years after AI initiation [14].

Our results demonstrated that arthralgia scores were significantly associated with noncompliance at 6 and 9 months post-study start, suggesting that over time arthralgia can have a negative impact on patient compliance. Although statistical significance was observed, clinical significance needs to be established. There appears to be a general consensus that a 30% reduction in pain intensity, equivalent to ‘much improved’ or ‘very much improved’ on a global impression of change, may be considered clinically significant [15]. As such, it may be assumed that a similar parameter would apply for an increase in pain intensity to be considered clinically relevant. However, this benchmark needs to be confirmed in future studies [15]. In addition, although musculoskeletal symptoms have been reported as the primary patient-reported reason for AI discontinuation [16], it is unknown if arthralgia intensity has a greater impact on patient compliance than arthralgia incidence. Other factors potentially influencing adherence include extremes of age (older or younger), increasing out-of-pocket costs, follow-up care with a general practitioner (versus oncologist), higher cytochrome P450 2D6 activity, and switching from one form of therapy to another [17]. This is of concern as low adherence has been associated with an increase in all-cause mortality [4]. Interestingly, arthralgia and musculoskeletal symptoms may be positively associated with clinical outcomes following endocrine therapy, reflected by a significant improvement in overall [18–20]. Similar findings have also been reported in a retrospective analysis of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [2]. The most frequently reported factors thought to improve compliance with oral medications include educating patients on adherence (taking medication as instructed and clinical outcomes) and better management of treatment-related AEs [21]. Prospective data on the extent of compliance and reasons for noncompliance in postmenopausal women with early breast cancer receiving anastrozole as an initial adjuvant therapy are reported in the Patient’s Anastrozole Compliance to Therapy (PACT) program [22]. In contrast to previous evidence [21], educational materials used in PACT did not significantly improve compliance with anastrozole therapy [22, 23], suggesting that direct discussion between physicians and patients is essential in achieving optimal compliance. Results from one study suggested that oncologists do not sufficiently discuss the importance of adherence to adjuvant endocrine therapy with patients [24]. Thus, it is recommended that oncologists educate patients on potential drug-related AEs, clinical outcomes, and the importance of adherence, to help manage expectations and beliefs about therapy. Furthermore, awareness of the potential relationship between joint symptoms and therapy response may help inform patients and improve long-term adherence [2]. Psychological home support, training in taking medication, and monitoring by pharmacists have all been shown to improve patient compliance in other diseases [25, 26]. Management of psychological factors may be helpful; depression and stressful life events were identified as major predictors for pain deterioration in women receiving successful non-AI treatment for early breast cancer [27].

We showed that investigators reported a lower incidence of arthralgia and higher estimated rates of compliance with
as arthralgia, arthritis, and muscle pain. The Arthralgia Working Group has developed a step-wise treatment algorithm for AI-induced arthralgia management, including the use of anti-inflammatory agents with additional analgesia where necessary [29]. It has been reported that the use of analgesics to manage AEs does not influence patient compliance with therapy [11]. In addition, arthralgia management should be conducted in collaboration with rheumatologists [30].

The arthralgia assessment techniques used in COMPACT, including RASQ, assessed both arthralgia pain and incidence. Thus, this study provides accurate and informative results contributing to the understanding of healthcare professionals involved in the management of women with breast cancer experiencing AI-induced arthralgia. There were some limitations to the study. Although patients were not actively excluded if they were not compliant with anastrozole therapy in the 3–6 months before study start, it is likely that they were not included because of the lack of patient interest or the physicians did not consider them appropriate for inclusion in the study. This may have caused bias toward more compliant patients and those with milder arthralgia symptoms. Furthermore, there was no active investigation of patients who were lost to follow-up during the study to determine reasons for discontinuation and as such we are unable to comment on whether this discontinuation was related to arthralgia. In addition, arthralgia and other musculoskeletal complaints were not specifically defined, and patients with osteoporosis were included. The various approaches to quantifying compliance among studies should be considered when comparing results.

In conclusion, data from the COMPACT may help inform patients and healthcare providers about the importance of arthralgia in the clinical management of women with early breast cancer and, therefore, contribute to the improvement of patient compliance and treatment outcomes.

acknowledgements

Final approval of the manuscript lay solely with the authors. The authors thank the patients, investigators, and health insurance agencies who participated in this study.

funding

The study was funded by AstraZeneca and supported by three major German health insurance funds (QWQ Service Plus AG, Techniker Krankenkasse, and Deutsche Angestelltenkrankenkasse). Medical writing services were provided by Emma Burke of iMed Comms, Macclesfield, UK and were funded by AstraZeneca.

disclosure

PH received funding for acting as a consultant or advisor from AstraZeneca. WB received honoraria for consultancy from Abbott, AstraZeneca, Janssen, and Merck Sharp & Dohme. CJ received honoraria from AstraZeneca for being a member of the AstraZeneca Speakers Bureau. MB and NH received honoraria for consultancy from AstraZeneca. PK received financial support for performing the statistical analysis from

<table>
<thead>
<tr>
<th>Table 2. Summary of adverse events and most frequent adverse events (&gt;0.5% of patients) in the safety population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upfront group (n = 1916)</strong></td>
</tr>
<tr>
<td><strong>Adverse event, number of patients (%)</strong></td>
</tr>
<tr>
<td>Any AE</td>
</tr>
<tr>
<td>Drug-related AE</td>
</tr>
<tr>
<td>Any serious AE</td>
</tr>
<tr>
<td>Drug-related serious AE</td>
</tr>
<tr>
<td>AE leading to treatment discontinuation</td>
</tr>
<tr>
<td>Death due to AE</td>
</tr>
<tr>
<td>Death due to other reason (progression of primary disease)</td>
</tr>
<tr>
<td><strong>Preferred term</strong></td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Hot flush</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Bone pain</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Alopeia</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Weight increased</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Pain in extremity</td>
</tr>
<tr>
<td>Lymphedema</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Arthropathy</td>
</tr>
<tr>
<td>Dry mouth</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Nail disorder</td>
</tr>
</tbody>
</table>

*aCausal relationship between anastrozole and AE = yes.
*bOne patient had a serious AE that was not included in the AE analysis; there was no entry in the AE database and this finding was unresolved at the time of data analysis.
*cDeath (n = 2), colon cancer (n = 1), malignant ascites (n = 1), pain (n = 1), brain metastases, and multiorgan failure (n = 1), exitus letalis in the scope of a decompensated heart failure (n = 1).
*dPatients were not included into the AE analyses (death not related to an AE). AE, adverse event.
AstraZeneca. SZ is an employee of AstraZeneca. HJH, KK, RK, WR, and DW have declared no conflicts of interest.

**references**