Compliance, Analgesic Use and Side-effect Protection within a German Cohort of the TEAM Trial

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Abstract. *Background: Compliance is an essential aspect for the success of any medical intervention. Adverse events (AEs) contribute significantly to non-compliance with endocrine treatment. The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial compared five years of adjuvant exemestane therapy with the sequence of tamoxifen followed by exemestane. Patients and Methods: A retrospective analysis of the German cohort of TEAM was conducted to determine the effects of prior tamoxifen on the tolerability profile of exemestane in both treatment arms. Results: Fracture incidence was significantly higher during the first 30 months of exemestane versus the 30 months of exemestane following tamoxifen for 2-3 years; however, the incidence of AEs was not significantly different. With regard to compliance, the use of analgesics did not influence overall or disease-free survival (DFS) nor the incidence of distant recurrence in both treatment groups. Conclusion: Tamoxifen has a boneprotective effect when applied before exemestane treatment. Intake of analgesics (or pain medication) does not influence compliance or treatment outcome.*

Adjuvant endocrine therapies have been proven to be effective treatment options for post-menopausal women with hormone receptor-positive breast cancer. Five years of adjuvant tamoxifen has been the standard-of-care in adjuvant endocrine treatment of women with breast cancer for many years. Recently, aromatase inhibitors (AIs), such as anastrozole, letrozole and exemestane, have demonstrated superior efficacy *versus* tamoxifen-alone for five years, when given as upfront adjuvant therapy or following two to three years of tamoxifen therapy (1-4). Current treatment guidelines recommend that an AI should be included in the endocrine treatment concept for the majority of post-menopausal patients with hormone receptor-positive breast cancer (5-7).

Women receiving endocrine therapy may experience treatment-related side-effects that negatively influence their quality of life (QOL) and therefore treatment. It is well-known, that adverse events (AEs) constitute the main reason for non-adherence to endocrine treatment. Side-effects can often be managed by additional treatments and this could lead to improved compliance and efficacy of the therapy (8). In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, discontinuation rates were significantly higher for tamoxifen compared to anastrozol (14.3% *versus* 11.1%, respectively, p=0.0002) (1).

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial compared adjuvant therapy with upfront exemestane for five years with the sequence of tamoxifen followed by exemestane for a total of five years of endocrine therapy (9). The final analysis of the TEAM trial showed no significant differences in disease-free (DFS) or overall survival (OS) between exemestane-alone and the sequence of tamoxifen followed by exemestane (9). There were differences in tolerability profiles between the two treatment arms: however exemestane monotherapy was associated with a higher incidence of musculoskeletal AEs, hypertension and hyperlipidaemia, compared to sequential treatment. Gynaecological abnormalities and venous thrombosis were observed more frequently with sequential treatment than with exemestane alone. Discontinuation rates were significantly higher in the sequential treatment arm (56.0% *versus* 29.6%, respectively) (9).

Here, we present results of a retrospective, exploratory analysis of the German cohort of the TEAM trial to assess if the use of analgesics during exemestane monotherapy had any impact on compliance with therapy and clinical outcome. Finally, we assessed if previous therapy with tamoxifen in the sequential treatment arm affected the tolerability profile of exemestane compared with the exemestane-alone arm.

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Key Words: Aromatase inhibitor, compliance, analgesics, exemestane, adverse events, TEAM trial.

Patients and Methods

The TEAM trial was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committees. Written informed consent was obtained from all patients.

Study design. TEAM was a large, multinational, randomised, open-label phase III trial evaluating the efficacy and safety of five years of exemestane 25 mg daily *versus* tamoxifen 20 mg daily for 2.5-3 years followed by exemestane for 2-2.5 years. Patients were randomised 1:1 to receive tamoxifen or exemestane. Patients started endocrine treatment within 10 weeks of the completion of surgery and chemotherapy, if indicated. The trial was conducted in Belgium, France, Germany, Greece, Ireland, Japan, the Netherlands, the United Kingdom and the United States.

A retrospective analysis of patients who were enrolled in the TEAM trial in Germany was performed to assess the effect of chemotherapy on the efficacy of endocrine therapy, to evaluate the use and impact of analgesics in patients receiving exemestane monotherapy, and to compare the safety of exemestane when given as monotherapy *versus* that given after 2-3 years of tamoxifen. Full details of the TEAM trial design, methodology and primary and secondary endpoints of the trial have been published previously (9). The German subgroup trial used for this analysis is registered with Ethics Commission Trial, 27/2001.

Assessments. Patients were assessed every three months during the first year of treatment and at least annually thereafter; mammography was performed each year. AEs were recorded at every visit using elicited responses; pre-printed checklists were not utilised. Pre-existing AEs were only included if they worsened after the first dose of the study drug. Severity of AEs was assessed by investigators, using the National Cancer Institute Common Toxicity Criteria version 2.0 (10) and AEs were coded centrally, using the Medical Dictionary for Regulatory Activities (version 12.1) (11). The use of analgesics by patients was also recorded.

Endpoints. This retrospective analysis assessed the use of analgesics by patients and the impact of analgesic use on OS, DFS, distant recurrence and compliance was evaluated. The AE profile of exemestane monotherapy during months 0-30 was compared with that of exemestane following tamoxifen therapy (during months 30-60). Our hypothesis was that prior treatment with tamoxifen would alter the type and incidence of AEs observed during subsequent treatment with exemestane as compared with exemestane monotherapy. AEs of interest included those associated with tamoxifen treatment (thrombosis and gynaecological abnormalities) or AI treatment (osteoporosis and fracture).

Statistical analysis. All patients who received at least one dose of study medication and had at least one follow-up assessment or experienced an event were evaluable for this analysis. OS, DFS and time-to-distant recurrence were calculated using Kaplan-Meier estimates. These efficacy endpoints were compared using the log-rank test. Fisher's exact test and the Chi-squared test were used to evaluate differences in proportions. All tests were two-sided and distribution-free, with statistical significance set at the 5% level. All database management and statistical analyses were carried out using Statistical Analysis System version 9.2 (SAS Institute Inc., Cary, NC, USA).

Table I. *Baseline characteristics of evaluable patients*.

Characteristic	Tamoxifen → exemestane (n=632)	Exemestane (n=610)	*p*-Value*
Mean age, years (SD)	63.1 (8.3)	62.9 (8.6)	0.67
Histological grade, n (%)			0.43
1	22 (3.5)	20 (3.3)	
2	479 (75.8)	460 (75.4)	
3	124 (19.6)	128 (21.0)	
Unknown	7 (1.1)	2 (0.3)	
Tumour (T) stage, n (%)			0.11
T1	380 (60.1)	354 (58.0)	
T2	201 (31.8)	220 (36.1)	
T3	23 (3.6)	22 (3.6)	
T4	28 (4.4)	14 (2.3)	
Nodal (N) stage, n (%)			0.04
N0	395 (62.5)	394 (64.6)	
N1	188 (29.8)	182 (29.8)	
N2	26 (4.1)	28 (4.6)	
N3	17 (2.7)	4 (0.7)	
NX	6 (1.0)	2 (0.3)	
Oestrogen receptor status, n (%)			0.26
Negative	24 (3.8)	16 (2.6)	
Positive	608 (96.2)	594 (97.4)	
Progesterone receptor status, n (%)			0.81
Negative	91 (14.4)	91 (14.9)	
Positive	541 (85.6)	519 (85.1)	
Prior surgery, n (%)			0.01
Breast conserving	409 (64.7)	437 (71.6)	
Mastectomy	222 (35.1)	173 (28.4)	
Other	1 (0.2)	-	
Adjuvant radiotherapy, n (%)			0.85
No	161 (25.5)	159 (26.1)	
Yes	471 (74.5)	451 (73.9)	
Prior chemotherapy, n (%)			0.52
No	329 (52.1)	310 (50.8)	
Yes	303 (47.9)	300 (49.2)	
Anthracycline	209 (33.1)	207 (33.9)	
CMF	65 (10.3)	73 (12.0)	
Other	29 (4.6)	20 (3.3)	

*Fisher's exact test to compare treatment groups (tamoxifen/exemestane versus exemestane-alone).

Results

Patients' characteristics. A total of 1502 patients were enrolled in the TEAM trial in Germany (739 received tamoxifen followed by exemestane and 763 received exemestane alone). Out of these, 1242 patients were evaluable for this analysis (632 patients in the tamoxifen followed by exemestane arm and 610 in the exemestane-alone arm). A total of 260 patients who did not receive at least one dose of study medication or did not have any follow-up assessments were excluded from the analysis.

Table II. *Overall survival (OS), disease-free survival (DFS) and distant recurrence in patients who did or did not receive analgesics in the exemestane monotherapy treatment arm* and in patients treated with tamoxifen followed by exemestane‡.*

	Tamoxifen → exemestane			Exemestane monotherapy		
	Analgesics used (n=180)	No analgesics used (n=451)	*p*-Value†	Analgesics used (n=235)	No analgesics used (n=369)	*p*-Value†
Deaths, n (%)	14 (7.8)	42 (9.3)	*p*=0.54	26 (11.1)	29 (7.9)	*p*=0.18
DFS events, n (%)	33 (18.3)	93 (20.6)	*p*=0.52	42 (17.9)	61 (16.5)	*p*=0.67
Distant recurrence events, n (%)	13 (7.2)	38 (8.4)	*p*=0.62	16 (6.8)	24 (6.5)	*p*=0.88

Analgesic use unknown for * 6 patients; ‡for 1 patient; †Chi-squared test to compare the group who had received analgesics *versus* the group who had not.

Baseline characteristics of patients are shown in Table I. Characteristics were generally similar across both treatment groups with significant differences between groups observed only with respect to prior surgery and the regional lymph node status (N) in the TNM classification (p=0.01 and p=0.04, respectively).

Effects' of analgesic use on OS, DFS and distant recurrence. In the exemestane arm, 235 patients (38.5%) received analgesics during therapy and 369 patients (60.5%) did not. Analgesic use was unknown for six patients (1%; Table II). A total of 180 patients (28.4%) treated with tamoxifen followed by exemestane received analgesics during treatment and 451 patients (71.4%) did not. Analgesic use was unknown for one patient (0.2%; Table II). The type of analgesics used and their prevalence within the treatment groups are described in Table III.

OS, DFS and the incidence of distant recurrence were not significantly different between patients who had received analgesics during exemestane therapy or tamoxifen followed by exemestane therapy and those who had not received analgesics (Table II). A total of 189 (80.4%) of patients who received analgesics were compliant with exemestane monotherapy compared to 292 patients (79.1%) who did not. A total of 137 (76.1%) of patients who received analgesics were compliant with tamoxifen followed by exemestane therapy compared with 352 patients (78.1%) who did not. There was no significant difference in compliance between those who received analgesics and those who did not in either treatment group.

Safety. The incidence of fractures was significantly higher during months 0-30 in patients with exemestane therapy than during months 30-60 with exemestane following tamoxifen (p=0.0158; Table IV). The fracture rate during the sequential treatment was higher during the tamoxifen treatment in months 0-30 (1.3%) than during the exemestane treatment in months 30-60 (0.73%). The incidence of other AEs was not significantly different between the monotherapy (months 0-30) and sequential therapy (months 30-60; Table IV) groups. Commonly reported AEs during exemestane treatment in the sequential arm were similar to those reported in the exemestane arm, and included arthralgia, osteoporosis and hypertension. AEs during tamoxifen treatment (months 0-30 of sequential treatment) were as expected based on the known safety profiles. AEs reported more frequently during tamoxifen than exemestane treatment included endometrial pathology, vaginal bleeding and thrombosis (Table IV).

Table III. *Classification and distribution (n, %) of analgesics used per treatment group.*

Class of Analgesic	Tamoxifen → exemestane (n=180)	Exemestane (n=235)
Non-steroidal anti-inflammatory drug (NSAID)	224 (72.73)	388 (77.60)
Opioid	44 (14.29)	52 (10.40)
Antidepressant	20 (6.49)	30 (6.00)
Anticonvulsant	5 (1.62)	7 (1.40)
Muscle relaxant	5 (1.62)	5 (1.00)
Other	10 (3.25)	18 (3.60)
Total number of analgesics	308 (100)	500 (100)

Discussion

The results from this retrospective analysis of the TEAM trial in Germany showed that OS, DFS and distant recurrence were similar between patients who had undergone sequential therapy and those who had undergone exemestane therapy only.

Compliance with endocrine therapy, as with therapy for other chronic diseases, has been shown to be suboptimal. Studies evaluating adherence to tamoxifen have shown that

Table IV. *Adverse events (AEs) during sequential treatment with tamoxifen and exemestane, and exemestane monotherapy.*

Adverse event, n (number per 100 women-years)	Tamoxifen → exemestane		Exemestane	*p*-Value*
	Months 0-30 (n=739)	Months 30-60 (n=493)	Months 0-30 (n=763)	
Gynaecological				
Endometrial pathology	6 (0.32)	0 (0.0)	1 (0.1)	1.0000
Vaginal bleeding	18 (1.0)	8 (0.7)	10 (0.5)	0.6363
Vaginal dryness	11 (0.6)	8 (0.7)	10 (0.5)	0.6363
Cardiovascular				
Arrhythmia	4 (0.2)	3 (0.2)	11 (0.6)	0.2704
Hypertension	39 (2.1)	50 (4.1)	56 (2.9)	0.0959
Thrombosis	20 (1.1)	5 (0.4)	6 (0.3)	0.7599
Musculoskeletal				
Arthralgia	110 (6.0)	145 (11.8)	223 (11.7)	0.9495
Fracture	24 (1.3)	9 (0.73)	33 (1.7)	0.0158
Osteoporosis	17 (0.9)	26 (2.11)	45 (2.4)	0.7081
Other				
Loss of libido	1 (0.1)	0 (0.0)	3 (0.2)	0.2841
Nerve compression	35 (1.9)	24 (2.0)	51 (2.7)	0.2226
Sleep disturbance	17 (0.9)	24 (2.0)	49 (2.6)	0.2686

*Fisher's exact test comparing tamoxifen/exemestane month 30-60 *versus* exemestane alone (months 0-30).

30-50% of patients did not complete the five-year course of treatment (12, 13). Similarly, adherence to AI treatment has also been shown to be suboptimal (14). Reasons for poor compliance are complex and may be related to sociodemographic factors, such as age or treatment-related factors, such as the occurrence of AEs (14). Two trials recently showed that educational material provided to post-menopausal women with hormone receptor-positive breast cancer under endocrine treatment with AI did not significantly improve their compliance with therapy (15, 16). However, regular patients attendance at follow-up visits, their participation in a cancer rehabilitation program and being a housewife or retired rather than being employed/unemployed significantly influenced compliance at 24 months (15, 16). The authors conclude that written information cannot sufficiently replace direct communication between patient and physician (16).

The use of analgesics during therapy may reduce the impact of AEs on patients, thus potentially improving the compliance with therapy. Results of our analysis showed that the majority of patients did not receive analgesics during endocrine therapy (60.5% in the exemestane arm and 71.4% in the sequential arm). Intake of analgesics neither influenced compliance nor OS, DFS or the incidence of distant recurrence, indicating that pain is not a main reason for non-compliance with endocrine therapy and does not influence the outcome.

Tamoxifen and AIs have different mechanisms of action. Tamoxifen is a selective estrogen modulator which prevents the binding of estrogen to its receptor, but also has a tissue-dependent partially agonistic effect (14). In contrast, AIs inhibit the conversion of androgen to estrogen, thus preventing the production of estrogen (16). As such, tamoxifen and AIs are associated with distinct safety profiles. Previous sub-studies from the TEAM trial have shown that while tamoxifen is associated with improved bone health (increased bone mineral density and decreased bone turnover) (18, 19) it is also associated with gynaecological AEs, such as endometrial thickening (20). In contrast, exemestane treatment is associated with bone loss and increased bone turnover (18, 19) but significantly less endometrial thickening. Additionally, previous studies have also shown that there are differences in AE profiles between sequential treatment with tamoxifen and an AI *versus* AI treatment alone (4, 9). Sequential treatment is associated with gynaecological symptoms, such as vaginal bleeding, whereas AI treatment alone is associated with musculoskeletal AEs (4, 9). Our analysis showed that the incidence of fracture was significantly lower during months 30-60 with exemestane following tamoxifen therapy *versus* months 0-30 of exemestane monotherapy. Tamoxifen has been shown to have a positive effect on bone health in post-menopausal women, resulting in increased bone mineral density (21) and reduced fracture risk compared with AIs (18, 22). Therefore, patients undergoing therapy with tamoxifen may have experienced an increase in bone mineral density, thus reducing the risk of fracture before patients switched to exemestane. Interestingly, the group of patients on sequential treatment had a higher incidence of fractures during the tamoxifen treatment than

during the exemestane treatment. This is probably due to the delayed onset of the therapeutic effect of tamoxifen. However, there was no significant difference in the incidence of other AEs between exemestane monotherapy (months 0-30) and exemestane following tamoxifen (months 30-60).

Our study is limited by the retrospective design and the small patient numbers included in the analysis. Consequently, the results should be interpreted with caution and should be considered hypothesis-generating. Additionally, the open-label design of the TEAM trial may have resulted in bias, particularly for the subjective reporting of AEs. The side-effect profiles of tamoxifen and exemestane are well-defined in such way that physicians and patients would have known which AEs to expect during treatment. High rates of discontinuation were observed during the TEAM trial, particularly during treatment with tamoxifen, with 40% of patients not completing at least five years of follow-up (9). It was suggested that this might have been due to results published during the trial, which indicated that AIs were more effective than tamoxifen. As such, physicians and patients may have switched early to exemestane or discontinued allocated therapy (9).

In conclusion, our results indicate that the known bone-protective effect of tamoxifen might also reduce the fracture risk during exemestane treatment when used sequentially in therapy of post-menopausal women with hormone receptor-positive breast cancer. Additionally, the majority of patients did not receive analgesics during endocrine therapy. Analgesics, taken during the endocrine treatment to reduce AEs, seemed not to improve compliance. Hence pain does not seem to be the main reason for non-compliance as compliance was not significantly different between patients who had or had not received analgesics during therapy.

Conflicts of Interest

M. Bossart has no conflicts of interest to declare. M. Becker has no conflicts of interest to declare. P. Hadji is currently conducting research sponsored by Pfizer and has given lectures for Pfizer. D. G. Kieback is currently conducting research sponsored by Pfizer and is a member of Pfizer's speakers bureau. A. Hasenburg has received honoraria from Pfizer for lectures and support for travel expenses to meetings.

Acknowledgements

Medical writing assistance was provided by Caroline Masterman at ACUMED (Tytherington, UK) and was funded by Pfizer, Inc.

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Received May 16, 2012
Revised August 1, 2012
Accepted August 2, 2012