Correlation of Treatment-emergent Adverse Events and Clinical Response to Endocrine Therapy in Early Breast Cancer: A Retrospective Analysis of the German Cohort of TEAM

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Introduction

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial was a phase III, randomized, open-label trial in which postmenopausal women with hormone receptor-positive early breast cancer were randomly assigned 1:1 to receive 25 mg of exemestane daily for 5 years or tamoxifen 20 mg daily for 2.5–3 years followed by 2–2.5 years of exemestane. TEAM was conducted in nine countries (Belgium, France, Germany, Greece, Ireland, Japan, the Netherlands, the United Kingdom and the United States). At a median follow-up of 5 years, after accrual of 9775 women, no significant differences in efficacy between 5 years' exemestane and the sequence of tamoxifen followed by exemestane was reported. We performed a retrospective analysis of the German cohort of the TEAM trial to investigate if the occurrence of specific treatment-emergent AEs was associated with clinical response to treatment with either tamoxifen or exemestane.

Methods

This was a retrospective analysis of all patients enrolled in the German cohort of the TEAM trial, to assess if there was any correlation between specific AEs and clinical outcome.

The occurrence of arthralgia and myalgia, fractures and menopausal symptoms were assessed every 3 months, and at least once-yearly thereafter; mammography was performed annually. In accordance with international guidelines, menopausal symptoms were defined as: hot flashes/flushes; constitutional symptoms, including difficulties sleeping, disorders of sleep, sleeping disturbances, sleeplessness, trouble with sleep, worsening sleep disturbance; insomnia; mood alteration-anxiety, agitation; mood alteration-depression; depressed level of consciousness. Data on AEs were obtained using elicited responses and pre-existing AEs were only included if they worsened following the first dose of study drug. Severity was assessed by the investigators, based on the National Cancer Institute Common Toxicity Criteria version 2.0.

Modifications to dose or schedule were not permitted. Patients discontinued study drug if the investigator considered it was medically necessary, unacceptable toxicity was experienced, consent was withdrawn or relapse of disease occurred. All patients were followed-up, whether or not they discontinued treatment. Adjuvant hormonal treatment was initiated within 14 weeks after completion of surgery. Patients completed a "Drug Administration Record" at home, which was brought to each clinic visit to document treatment compliance.

Endpoints for this analysis were disease-free survival (DFS) and overall survival (OS) in patients with and without arthralgia and myalgia and those with and without menopausal symptoms.

Statistical analysis

All randomized patients who started treatment were included in the intention-to-treat population. The intention-to-treat population was used for all efficacy analyses. Kaplan-Meier estimates were used to calculate OS and DFS in patients with and without arthralgia/myalgia, those with and without menopausal symptoms.

Endpoints were compared using log-rank tests and all P-values were two-sided. P-values <.05 were considered statistically significant. All database management and statistical analyses were carried out using the Statistical Analysis System version 9.1.

*Height was only measured in 563 patients in the tamoxifen arm and 650 patients in the exemestane arm
**Weight was only measured in 622 patients in the tamoxifen arm and 640 patients in the exemestane arm
†BMI could only be calculated in 481 patients in the tamoxifen arm and 551 patients in the exemestane arm
‡Only 67 patients in the tamoxifen arm and 77 patients in the exemestane arm had a transvaginal ultrasound result

Results

A total of 1525 patients were randomized to tamoxifen (n=752) or exemestane alone (n = 773). A total of 23 patients did not start treatment; therefore, 739 patients and 763 patients were included in this analysis, respectively. Overall, baseline characteristics of patients were similar across treatment groups (Table 1). The incidence of arthralgia or myalgia and menopausal symptoms at baseline was similar between groups (data not shown).

	Tamoxifen→ Exemestane (n=739)	Exemestane (n=763)	P-value
Mean age, years (SD)	63.3 (8.2)	63.2 (8.4)	.7498
Mean height, cm (SD)*	163.7 (6.0)	163.6 (6.1)	.8121
Mean weight, kg (SD)**	71.56 (13.43)	70.93 (12.70)	.3944
Mean BMI, kg/m2 (SD)†	26.79 (5.03)	26.38 (4.61)	.1795
Mean endometrium thickness, mm (SD)‡	3.1 (1.5)	2.7 (1.4)	.1034
Adjuvant chemotherapy, n (%)	338 (45.74)	364 (47.71)	.4448
Previous radiotherapy, n (%)	563 (76.18)	582 (76.28)	.9660
Tumour grade, n (%)			
Grade 1	26 (3.52)	26 (3.41)	.9067
Grade 2	558 (75.51)	582 (76.28)	.7273
Grade 3	148 (20.03)	152 (19.92)	.9592
Not assigned	7 (0.95)	3 (0.39)	.1900
Tumour stage, n (%)			
Stage 1	444 (60.08)	444 (58.19)	.4567
Stage 2	241 (32.61)	277 (36.30)	.1325
Stage 3	24 (3.25)	25 (3.28)	.9749
Stage 4	30 (4.06)	17 (2.23)	.0425

Figure 1: DFS in patients with and without arthralgia/myalgia

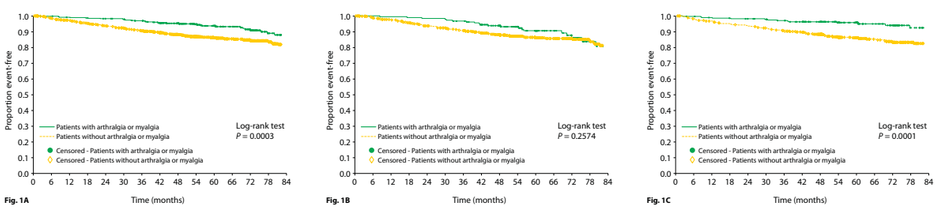

Fig. 1A Fig. 1B Fig. 1C

In the total patient population, patients who experienced arthralgia/myalgia had significantly longer DFS (P = .0003; Fig 1A) than those who did not report these symptoms. There was no difference in DFS in tamoxifen-treated patients with or without arthralgia/myalgia (P = .2574; Fig 1B). DFS was significantly improved in exemestane-treated patients with arthralgia/myalgia versus those without this AE (P =.0001; Fig 1C).

Figure 2: OS in patients with and without arthralgia/myalgia

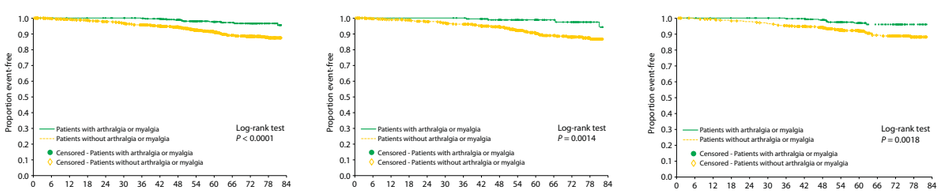

Fig. 2A Fig. 2B Fig. 2C

In the total patient population, patients who experienced arthralgia/myalgia had significantly longer OS (P < .0001; Fig 2A) than those who did not report these symptoms. The improvement in OS was irrespective of treatment, with OS significantly improved in both tamoxifen- and exemestane-treated patients reporting arthralgia/myalgia versus those with no arthralgia/myalgia (P =.0014 and P = .0018; Figs 2B and 2C).

Figure 3: DFS in patients with and without menopausal symptoms

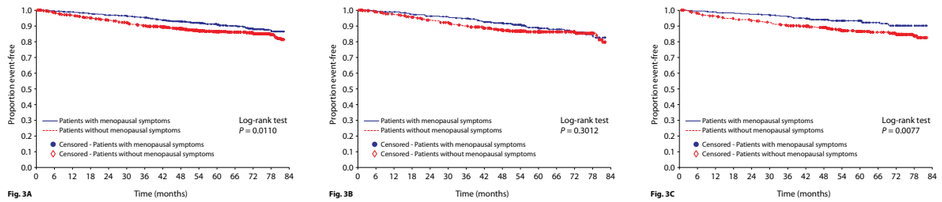

Fig. 3A Fig. 3B Fig. 3C

DFS was significantly longer in patients reporting menopausal symptoms compared with those who did not report these symptoms (P = .0110; Fig 3A). There was no significant difference in DFS between tamoxifen-treated patients with or without menopausal symptoms (Fig 3B). The improvement in DFS in patients with menopausal symptoms was only observed in patients receiving exemestane. Exemestane-treated patients reporting menopausal symptoms had significantly longer DFS than those not reporting menopausal symptoms (P = .0077; Fig 3C).

Figure 4: OS in patients with and without menopausal symptoms

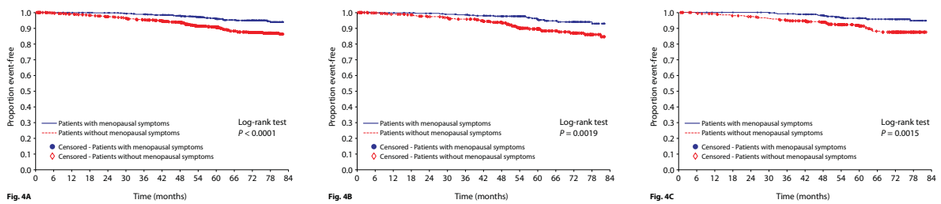

Fig. 4A Fig. 4B Fig. 4C

In the total patient population, OS was significantly longer in patients reporting menopausal symptoms compared with those who did not report menopausal symptoms (P < .0001; Fig 4A). OS was significantly improved in both tamoxifen- and exemestane-treated patients who experienced menopausal symptoms versus those who did not report these symptoms (P =.0019 and P = .0015, respectively; Figs 4B and 4C).

Discussion

This analysis suggests that patients reporting arthralgia/myalgia and those reporting menopausal symptoms had significantly longer DFS and OS than patients who did not report these AEs. The effect on OS was irrespective of treatment however the difference in DFS was only observed in exemestane-treated patients.

It may be that more effective inhibition of the estrogen receptor-positive breast cancer tumor also results in increased menopausal symptoms and joint symptoms due to a near total estrogen deprivation, as it is thought that these symptoms are related to this effect of endocrine therapy. However, further research into the mechanisms behind the correlation of the occurrence of these symptoms and response to endocrine therapy is required.

The occurrence of treatment related adverse events may result in poor adherence to therapy. These results may help reassure patients and encourage them to continue therapy, thereby improving adherence. Our results may also raise questions regarding the appropriateness of treating these AEs, as this may also have an effect on the efficacy of endocrine therapy. However, further investigation regarding this is required.

Limitations of our study include the inaccuracy of coding AEs and serious AEs in clinical trials, as well as the small (n = 1502) patient population. In addition, it is important to note that this was a retrospective analysis, and, as such, caution should be applied when interpreting these results.

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