

Under-reporting of Symptoms in Patients with Early Breast Cancer who have Received Tamoxifen Treatment for 2 to 3 years

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METHODS

- Symptoms reported at baseline in the patient Case Report Form (CRF) were recorded by CTC grade (Figure 1). Grades 1 & 2 and grades 3 & 4 have been combined. Symptoms have been divided into those explicitly listed on the CRF and those not specifically listed but recorded under 'other'.
- Quality of life was assessed using the FACT-ES questionnaire (items used here are given in figure 2). Patients are asked to endorse specific items 'not at all', 'a little bit', 'somewhat', 'quite a bit' or 'very much'.
- For this analysis 'a little bit' and 'somewhat' have been combined and compared to CTC grade 1 & 2; 'quite a bit' and 'very much' have been combined and compared to CTC grades 3 & 4; this gives 3-point ordinal scales for each method of assessment

- Differences in the distribution of severity of symptoms are compared between countries using chi-squared based tests

- Kappa statistics (see box) have been used to measure the degree of agreement between clinician assessed and patient reported symptoms at entry to the trial for symptoms where >10% patients reported 'quite a bit' or 'very much', plus those listed on the CRF.

Figure 1: Extract from IES CRF – signs/symptoms at baseline

Signs/Symptoms	None/CTC Grade 1-2	Somewhat/CTC Grade 3-4
Nausea (GU N/AU)		
Vomiting (GU VOM)		
Headaches (NE HEAD)		
Hot flashes (EM FLA)		
Vaginal bleeding (code as for GU HEM)		
Visual disturbances (NE VIS)		
Dizziness (NE DIZ)		
Insomnia (NE INS)		
Fatigue (FL LET)		
Sweating (FL SWE)		
Thrombo-embolic disease (CV EN)		
Other		

Figure 2: Symptom specific items and Endocrine subscale of the FACT ES QOL questionnaire

Below is a list of statements that other people with your illness have said are important. By circling one number per row please indicate how true each statement has been for you during the past 7 days. Please not feel nervous has been omitted

	None	A little	Somewhat	Quite a bit	Very much
1 I have a lack of energy	0	1	2	3	4
2 I have nausea	0	1	2	3	4
27 I sleep waking up	0	1	2	3	4

	None	A little	Somewhat	Quite a bit	Very much
3 I have hot flashes	0	1	2	3	4
39 I have vaginal discharge	0	1	2	3	4
42 I have vaginal itching/burning	0	1	2	3	4
43 I have vaginal bleeding or spotting	0	1	2	3	4
44 I have vaginal dryness	0	1	2	3	4
45 I have pain or discomfort with intercourse	0	1	2	3	4
46 I have hot interest in sex	0	1	2	3	4
48 I have gained weight	0	1	2	3	4
49 I feel light-headed/dizzy	0	1	2	3	4
50 I have been vomiting	0	1	2	3	4
51 I have diarrhoea	0	1	2	3	4
52 I get headaches	0	1	2	3	4
53 I feel bloated	0	1	2	3	4
54 I have breast sensitivity/tenderness	0	1	2	3	4
55 I have mood swings	0	1	2	3	4
56 I am irritable	0	1	2	3	4

INTRODUCTION

The Intergroup Exemestane Study (IES) is an international, double-blind, randomised phase III trial in postmenopausal women who have been taking tamoxifen for 2 to 3 years, comparing the study with tamoxifen to sequential exemestane giving a total of five years endocrine therapy.

The sub-study was a QOL sub-protocol which includes assessment of endocrine symptoms. Collection of QOL data continues for comparative analysis of patient reported QOL by treatment.

Endocrine therapies are generally viewed as a gentler, better-tolerated alternative to other breast cancer treatments. However, there is an often a difference in the frequency and severity of some of the side-effects reported by patient self-report.

556 patients have been recruited to the QOL sub-protocol from 33 centres in 8 countries: USA (27 patients), United Kingdom (163), Spain (47), Argentina (16), Italy (16), The Netherlands (4), New Zealand (2). Baseline characteristics of patients participating in the QOL sub-protocol have been previously reported.¹

At trial entry, there is a cohort of women who have been on tamoxifen for between two and three years.

This analysis examines discrepancies between patient and clinician symptom reporting at baseline.

RESULTS

Table 1: Frequencies of symptoms at entry to the trial

Symptoms	CTC grade	CRF	self-report	QOL score
hot flashes	1 & 2	45.2	35.3	a little bit & somewhat quite a bit & very much
weight gain	1 & 2	2.9	2.0	a little bit & somewhat quite a bit & very much
sweating (night sweats)	1 & 2	18.3	20.7	a little bit & somewhat quite a bit & very much
insomnia	1 & 2	18.2	0.4	a little bit & somewhat quite a bit & very much
fatigue	1 & 2	17.6	50.2	a little bit & somewhat quite a bit & very much
vaginal dryness	1 & 2	2.0	10.8	a little bit & somewhat quite a bit & very much
headaches	1 & 2	15.2	24.6	a little bit & somewhat quite a bit & very much
diarrhoea	1 & 2	0.5	14.2	a little bit & somewhat quite a bit & very much
nausea	1 & 2	20.3	0.7	a little bit & somewhat quite a bit & very much
short of breath	1 & 2	1.1	31.7	a little bit & somewhat quite a bit & very much
dizziness	1 & 2	0.5	26.1	a little bit & somewhat quite a bit & very much
vaginal bleeding	1 & 2	0.0	1.3	a little bit & very much

Symptoms with * are not specifically listed in the CRF but were reported under 'other'

Table 2: Frequencies of QOL symptoms not recorded on the CRF

Symptom	Self reported	QOL Score	Symptom	Self reported	QOL Score
bloating	36.0	a little bit & somewhat quite a bit & very much	vaginal discharge	29.9	a little bit & somewhat quite a bit & very much
breast tenderness	33.3	a little bit & somewhat quite a bit & very much	vaginal itching	24.8	a little bit & somewhat quite a bit & very much
cold sweats	17.8	a little bit & somewhat quite a bit & very much	irritable	6.6	a little bit & somewhat quite a bit & very much
mood swings	11.0	a little bit & somewhat quite a bit & very much	diarrhoea	5.2	a little bit & somewhat quite a bit & very much
muscle aches	48.2	a little bit & somewhat quite a bit & very much	joint pain	1.8	a little bit & somewhat quite a bit & very much
lymphoedema	9.7	a little bit & somewhat quite a bit & very much	vomiting	2.0	a little bit & somewhat quite a bit & very much
pain with intercourse	24.4	a little bit & somewhat quite a bit & very much			
	8.7	a little bit & somewhat quite a bit & very much			

There were some differences in the frequency distributions of both clinician and patient reported symptoms by country.

The distribution of clinician symptom scores differed significantly (p<0.01) by country for hot flashes, sweating, headaches and fatigue.

Levels of patient reporting differed significantly by country for hot flashes and fatigue and also insomnia, night sweats and vaginal dryness.

As an example, Figure 3 compares the clinician and patient reports of hot flashes by other countries.

Kappa (κ) statistics measure inter-rater agreement - here the degree of agreement between clinician assessed and patient reported symptoms at entry to the trial

- κ=1 indicates perfect agreement
- κ=0.8 indicates good agreement
- κ=0.5 indicates poor-fair agreement
- κ=0 with agreement = no better than chance
- Weighted κ takes into account the degree of misclassification
- Interpretation of kappa depends on number of categories and prevalence of the symptom across categories

Figure 3: Differential reporting of hot flashes

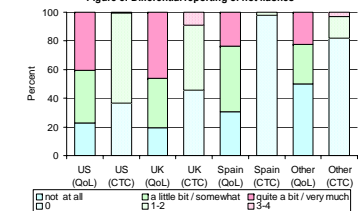


Table 3 shows the kappa statistics for scores of none versus any symptoms.

Table 3 Agreement between clinician and patient reporting of presence of symptoms

Symptom	% Prevalence		Kappa	95% CI
	CRF	QOL		
Symptoms listed on CRF				
Hot flashes	49.8	73.5	0.73	0.70 - 0.75
Insomnia	17.9	0.4	0.42	0.42 - 0.48
Headaches	16.8	40.7	0.68	0.63 - 0.69
Fatigue	21.0	71.5	0.44	0.41 - 0.47
Diarrhoea	0.5	14.2	0.68	0.67 - 0.70
Vaginal bleeding	2.7	5.4	0.97	0.96 - 0.98
Symptoms not explicitly listed on CRF				
Weight gain	2.9	73.3	0.29	0.26 - 0.31
Sweating (night sweats)	16.6	58.8	0.55	0.52 - 0.58
Decreased libido	0.4	0.2	0.37	0.34 - 0.40
Vaginal dryness	2.2	46.6	0.54	0.51 - 0.57
Shortness of breath	1.1	31.7	0.52	0.50 - 0.58

Weight gain and decreased libido show only fair agreement (kappa < 0.4) with much higher prevalence being reported directly by patients via the quality of life questionnaires than in their clinician during their baseline assessment.

Table 4 further assesses agreement by considering weighted kappas for 3 point severity scales.

Table 4: Agreement and kappa statistics for scoring of symptoms listed on CRF (3 point scale)

Symptom	Observed agreement	Expected agreement	Weighted kappa	95% CI
Symptoms listed on CRF				
Hot flashes	69%	50%	0.296	0.25 - 0.35
Insomnia	83%	0%	0.26	0.24 - 0.14
Headaches	80%	74%	0.205	0.14 - 0.23
Fatigue	63%	62%	0.027	0.06 - 0.11
Diarrhoea	83%	80%	0.028	0.11 - 0.23
Vaginal bleeding	97%	96%	0.025	0.25 - 0.38
Symptoms not explicitly listed on CRF				
Weight gain	47%	47%	0.017	0.00 - 0.02
Sweating (night sweats)	64%	59%	0.02	0.01 - 0.02
Decreased libido	56%	56%	0.002	0.00 - 0.01
Vaginal dryness	56%	56%	0.002	0.00 - 0.01
Shortness of breath	75%	75%	0.023	0.18 - 0.025

As expected, on average, there was significantly less agreement between clinician and patient reported scoring of symptoms for questions that were not explicitly listed on the CRF (mean kappa 0.04) versus symptoms that were (mean kappa 0.18, p<0.01)

Agreement for 'decreased libido' is no better than that expected by chance.

Table 5 shows weighted kappa statistics (3 point severity scales) by country for the top 3 recruiting countries to the Quality of Life study. Shaded cells indicate agreement is no better than by chance (1% significance level). Country specific frequencies for severe symptoms (CTC score 3 or 4 or patient 'quite a bit' or 'very much') are small thus comparisons are exploratory.

Table 5: Country specific kappa statistics (3 point scale)

Number with specific CRF	N=558 All patients		N=272 UK		N=166 US		N=233 Spain	
	Count	%	Count	%	Count	%	Count	%
Symptom listed on CRF								
Hot flashes	285	51%	315	55%	216	64%	354	62%
Insomnia	108	19%	116	41%	148	39%	225	62%
Headaches	105	19%	234	84%	282	70%	332	64%
Fatigue	287	51%	354	62%	341	70%	400	69%
Diarrhoea	168	30%	159	58%	287	70%	207	59%
Vaginal bleeding	325	58%	337	100%	385	92%	483	100%
Symptom not listed on CRF								
Weight gain	127	23%	124	45%	120	35%		
Sweating (night sweats)	282	50%	366	100%	350	100%		
Decreased libido	835	15%	208	75%	81	25%		
Vaginal dryness	835	15%	208	75%	81	25%		
Shortness of breath	835	15%	208	75%	81	25%		

- There is no significant difference between average kappa statistics by country
- There are some country differences in degree of agreement on specific symptoms.

CONCLUSIONS

Clinically severe symptoms (CTC grade 3 or 4) are not commonly reported in this cohort of women who have been on tamoxifen for 2 to 3 years

The current system of symptom collection, either with open questions or with collection of symptoms by positive list, leaves room for underreporting of symptoms of low clinical severity but high QOL impact.

Some important symptoms, in particular those to do with sexual issues, are self-reported by a significant proportion of women but are under-reported or not detected at clinical assessment

Lack of agreement / under-reporting could be due to patients not reporting symptoms to their clinician or differences in time period considered

clinicians not asking a complete range of questions or open-ended questions

We are investigating whether the method of CRF completion (e.g. timing of CRF completion relative to patient visit, method of ascertainment of degree of symptoms) further affects reporting of symptoms

There are some country differences in prevalence of symptoms and degree of agreement on specific symptoms which have implications for QOL studies with wide international participation, particularly for how data are extrapolated to different countries.

The use of specific QOL questionnaires helps in identifying underreported symptoms but careful clinical evaluation and inquiries on other symptoms pertaining to the psychological and social domains should be considered, particularly in low risk patients treated with hormones or other generally well tolerated regimens

References

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Acknowledgments

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