Endocrine-related symptoms during neoadjuvant endocrine therapy for breast cancer: Agreement between patient and physician reporting in a prospective clinical trial

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Background

There is a high risk of under-reporting of subjective toxicities by physicians, even when data is collected prospectively in clinical trials[1)]. It has been recommended to include patient-reported measures regarding symptoms in all prospective clinical comparative effectiveness trials in adult oncology[2)]. However, there have been few reports of agreement with respect to endocrine-related symptoms between patient and physician reporting in prospective clinical trials.

Patients and Method

The National Surgical Adjuvant Study of Breast Cancer 06 (N-SAS BC 06) is a multicenter, phase III randomized clinical trial of postmenopausal, hormone receptor-positive breast cancer patients, with a two-stage (preoperative and postoperative) enrollment, and intervention. The primary aim was to evaluate the need for adjuvant chemotherapy in the treatment of postmenopausal breast cancer patients who responded to neoadjuvant treatment with letrozole (LET) for 24-28 weeks. After surgery, responders were randomized into two arms receiving either chemotherapy plus LET, or LET alone after surgery. The primary endpoint was disease-free survival, and the secondary endpoints included adverse events, health-related quality of life (HRQoL) and health economic evaluation. We previously reported that neoadjuvant endocrine therapy with LET had no impact on global HRQoL, but that it did influence patient-reported endocrine-related symptoms such as hot flushes[3)].

In this study, the concordance rate between Clinician Reported Outcomes (CROs) and Patient Reported Outcomes (PROs) in their endocrine symptoms during neoadjuvant endocrine therapy was examined. Symptoms were collected prospectively by physicians (using the Japanese version of the Common Toxicity Criteria for Adverse Events [version 3.0] at enrollment, i.e., at baseline, and 4 and 16 weeks after starting neoadjuvant LET. Patients also completed the FACT-G (General), B (Breast), ES (Endocrine Symptoms), and HADS (Hospital Anxiety and Depression Scale). The endocrine symptoms according to the PROs, included nausea (GP2), hot flushes (ES1), cold sweats:(ES2), headaches (An10), and HADS-Depression score. In Functional Assessment of Cancer Therapy (FACT), “Not at all” was used to express the absence of the symptoms, and “A little bit”, “Some-what”, “Quite a bit”, and “Very much” were used to express the presence of symptoms. The HADS-Depression score threshold was 10/11[4)]. According to the CROs, grade 0 was defined as the absence of symptoms and grade 1 or more was defined as the presence of symptoms. Cohen's kappa coefficient was used to determine the concordance between CROs and PROs. The sensitivity of the CROs was also calculated.

Results

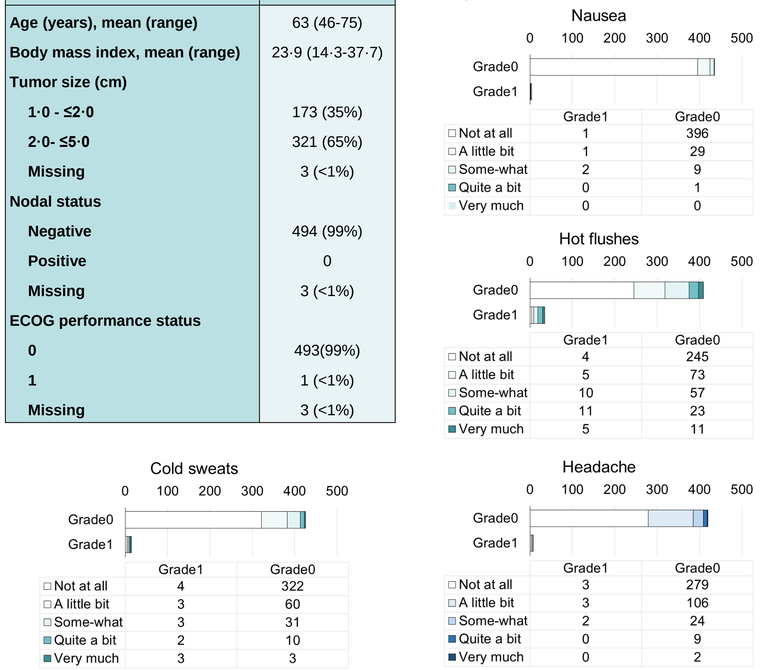
This study enrolled 497 subjects from the N-SAS BC 06 who were evaluated for PROs. The baseline demographics and clinical characteristics of subjects were shown in Table 1.

There were no physician reported grade 2 or more severe adverse events related to nausea, hot flushes, cold sweats, and headaches during neoadjuvant LET. The proportions of patients, who were graded 0 by physician, and reported “A little bit” or more severe symptoms were about 10% for nausea, 40% for hot flushes, 25% for cold sweats and 35% for headache (Figure 1).

Table 1. Baseline characteristics

Variable	Value
Age (years), mean (range)	63 (46-75)
Body mass index, mean (range)	23·9 (14·3-37·7)
Tumor size (cm)	
1·0 - ≤2·0	173 (35%)
2·0- ≤5·0	321 (65%)
Missing	3 (<1%)
Nodal status	
Negative	494 (99%)
Positive	0
Missing	3 (<1%)
ECOG performance status	
0	493(99%)
1	1 (<1%)
Missing	3 (<1%)

Figure 1. Distribution of CROs (CTC-AE) and PROs (items of FACT-B) 4 weeks after starting neoadjuvant LET.



The calculated point estimates of Cohen's kappa coefficient at Weeks 4 and 16 after starting neoadjuvant LET were 0.12 and 0.01 for nausea, 0.16 and 0.18 for hot flushes, 0.12 and 0.09 for cold sweats, 0.03 and 0.02 for headaches, and 0.11 and 0.11 for anxiety/depression, respectively; the concordance was quite low regardless of the types of symptoms and the observation time. The sensitivities of CROs at Weeks 4 and 16 after starting neoadjuvant LET were 0.07 and 0.03 for nausea, 0.16 and 0.17 for hot flushes, 0.1 and 0.08 for cold sweats, 0.03 and 0.03 for headaches, and 0.11 and 0.1 for dysthymia/depression, respectively; the sensitivity was quite low, regardless of the symptoms and observation time.

Table 2. Sensitivity, specificity and accuracy of CROs, and concordance between CROs and PROs

Adverse Event (AE)	Time Point	Number of: AE reported by neither patient nor physician	AE reported by patient but not physician	AE reported by physician but not patient	AE reported by both patient and physician	Sensitivity	Specificity	Accuracy	Cohen's κ: Point estimate
Nausea									
	Baseline	433	30	0	0	0.00	1.00	0.94	-
	4 weeks	396	39	1	3	0.07	1.00	0.91	0.12
	16 weeks	377	35	7	1	0.03	0.98	0.90	0.01
Hot flushes									
	Baseline	304	153	0	3	0.02	1.00	0.67	0.03
	4 weeks	245	164	4	31	0.16	0.98	0.62	0.16
	16 weeks	249	143	3	30	0.17	0.99	0.66	0.18
Cold sweats									
	Baseline	368	90	0	1	0.01	1.00	0.80	0.02
	4 weeks	322	104	4	11	0.10	0.99	0.76	0.12
	16 weeks	316	94	5	8	0.08	0.98	0.77	0.09
Headache									
	Baseline	315	142	2	1	0.01	0.99	0.69	0.00
	4 weeks	279	151	3	5	0.03	0.99	0.65	0.03
	16 weeks	277	135	3	4	0.03	0.99	0.67	0.02
Anxiety and Depression									
	Baseline	434	28	4	1	0.03	0.99	0.93	0.04
	4 weeks	421	17	8	2	0.11	0.98	0.94	0.11
	16 weeks	397	18	8	2	0.10	0.98	0.94	0.11

Discussion and Conclusion

This study showed that there were big differences between CROs and PROs in endocrine symptoms associated with endocrine therapy and that physicians could not obtain sufficient information regarding the endocrine symptoms. It is recommended that PROs be used to evaluate adverse events caused by endocrine therapy.

References

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QR Code

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