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Title: Self-evaluation of adjuvant chemotherapy-related side effects by patients with breast cancer

Subtitle: Patient-reported chemotherapy side effects

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Abstract

Importance: The patient's perspective on chemotherapy-related side effects is becoming increasingly acknowledged both in experimental clinical trials and in the clinical practice.

Objective: To evaluate how breast cancer patients receiving standard adjuvant chemotherapy report and grade side effects using a ten-item, paper questionnaire derived from the US National Cancer Institute's (NCIs) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and to compare patient with doctor reports.

Design, setting and participants: The questionnaire was administered to 604 patients at 11 sites after the first and third cycle of adjuvant chemotherapy between January 2011 and October 2013. CTCAE v4.0 definitions of grade of severity for nausea, vomiting, constipation, anorexia, dysgeusia, diarrhea, fatigue, pain, paresthesia, and dyspnea were translated into Italian and rephrased. Side effect information was also extracted from the medical charts to compare to patient-reported data.

Main outcomes and measures: Differences in side effects reporting between paired questionnaires were studied by the McNemar Test and the Wilcoxon signed rank test. Agreement between patient and doctor side effect reporting (grade 0 *vs.* grade ≥1) was studied using Cohen's kappa statistic. The effect of the number of patients enrolled at each Institution on the magnitude of discrepancy in side effect reporting between patients and doctors was studied by linear regression.

Results: 596 and 581 questionnaires were collected after cycles 1 and 3, respectively. A median of 82% of fields were filled in. A corresponding doctor questionnaire completed from chart data was available for 594 and 573 patient questionnaires. The frequency and severity of chemotherapy-related side effects were consistently greater in patient-reported than doctor-reported data. As a result, inter-rater agreement was low for most side effects,

ranging from 0.10 for anorexia to 0.51 for vomiting (Cohen's kappa statistic). There was a strong and significant positive correlation between the magnitude of the discrepancy in the frequency of reporting side effects and the number of patients enrolled at each site.

Conclusions and relevance: Adherence to reporting adjuvant chemotherapy-related side effects using the CTCAE system is high in women undergoing adjuvant chemotherapy for breast cancer. Workload may contribute to agreement discrepancies by limiting the doctor-patient relationship.

Introduction

Accurate reporting of treatment-related side effects is crucial for the appropriate management of cancer patients. In routine clinical practice, side effect reporting is pivotal in the decision-making process for dose modifications (e.g., dose reduction, treatment delay or withdrawal), supportive care administration, and prophylaxis. Side effect reporting (occurrence and grade of severity) is mandatory and highly standardized in clinical trials of new drugs or that compare newer treatments or regimens with an established gold standard [1-3]. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) is the most widely used protocol for the description and grading of treatment-related side effects in cancer therapy trials [4]. CTCAE items include laboratory abnormalities, objective clinical findings, and subjective side effects experienced by the patient during and/or after drug exposure. The collection, coding, and grading of patient-reported adverse events is usually based on information abstracted from the patient's medical records, making the use of a standardized system like the CTCAE demanding and resource-intensive for the clinical research team. Furthermore, the patient experience may not be fully captured by the physicians or nurses documenting clinical findings. Several papers from clinical trials have highlighted discrepancies in the side effects reported by medical staff and patients, with doctors frequently underestimating the incidence and severity of side effects [5-11]. Since underreporting of chemotherapy-related side effects is a problem even in the highly controlled clinical trial environment, it is likely to be even more pronounced in routine clinical practice, where reporting does not follow strict standards. Consequently, there is growing interest in including "patient-reported outcomes" (PROs) in a CTCAE-compliant manner, where PROs are subjective reports from patients without medical interpretation (e.g., quality of life questionnaires) [12-17].

Because the use of a standard reporting system like CTCAE in routine clinical practice is attractive, yet challenging to implement [18], we established a prospective study in

mid-2010 to evaluate how breast cancer patients receiving standard adjuvant chemotherapy report and grade side effects using a ten-item, paper questionnaire (hereinafter referred to as “questionnaire”). The questionnaire was derived from the CTCAE v4.0 definitions and converted to Italian. The side effects reported by patients were also compared to those described by the treating oncologists who were informed of, but not formally involved in, the study. To minimize bias from cancer-associated symptoms, women with non-metastatic breast cancer undergoing standard adjuvant chemotherapy after breast surgery were studied.

Patients and Methods

Eligibility criteria

Women aged 18 years or over who had undergone surgery for operable breast cancer and were candidates for first-time adjuvant chemotherapy outside a clinical trial were eligible for study. Patients were asked to fill in the questionnaire twice: first at the end of the first chemotherapy cycle (usually on the day scheduled for the second cycle of chemotherapy) and the second at the end of the third cycle (usually on day scheduled for the fourth cycle of chemotherapy). Patients completed the questionnaires in the waiting room. Since it has previously been shown that the timing of questionnaire completion with respect to seeing the oncologist does not introduce significant bias [5], patients were able to complete the questionnaires before or after visiting the treating oncologist but before administration of chemotherapy. Oncology staff provided no assistance with filling in the questionnaires, but a dedicated nurse at each center provided a detailed explanation of the questionnaire at the time of informed consent before the first cycle of chemotherapy. Furthermore, patients were provided with a diary to use at home, to facilitate documenting the onset and duration (in days) of side effects in relation to receiving chemotherapy. However, home diaries were not collected as part of the study material. Treating oncologists

were provided with study details (i.e., the items listed in the questionnaire) but were not formally involved in the design and execution of the study and were not notified of patients' participation in the study. The protocol was approved by the Ethical Committees of the participating Institutions. Each patient was required to sign an informed consent before entering the study.

Patient questionnaire

A ten-item paper questionnaire was developed in which the side effect definitions and severity grades were translated into Italian from CTCAE v4.0. The 10 items were: nausea, vomiting, constipation, anorexia, dysgeusia, diarrhea, fatigue, pain (generic), paresthesia, and dyspnea. These items were selected from a longer list due to their incidence in this group of patients, their considerable subjective component, and because they usually partially or completely resolve at the time of the next cycle of chemotherapy. Consequently, their reporting is unlikely to be consistent unless the patients are specifically asked.

The presence, grade, and duration of each item was recorded, with duration subdivided into day of onset, duration in days, and persistence at the time of questionnaire administration; i.e, five fields in total. A sample of the Italian questionnaire and its English translation are available in the on-line only supplemental material (eFigure 1 Appendix 1, respectively). Patients were asked to indicate if, after the previous chemotherapy administration, the side effect occurred. If the response was "yes" then patients indicated which of a set of statements best described their worst experience of that specific side effect, where each statement corresponded to the grades of severity described in CTCAE v4.0. For example, grade 2 nausea corresponded to "I felt nauseated and, because of that, I ate and drank less than usual". Finally, patients were asked to report the day of onset of each side effect with respect to the timing of previous chemotherapy (e.g., day 3; third day after chemotherapy administration), the duration of side effect in days (any severity), and/or

whether the side effect persisted at the time of completing the questionnaire. When the Italian translation of CTCAE v4.0 became available and was endorsed by the Italian Association of Medical Oncology in mid 2011 (available at: http://www.aiom.it/area+pubblica/area+medica/prodotti+scientifici/position+paper/CTCAE+in+the+pocket/1%2C1004%2C1%2C), the questionnaire was re-checked and no corrections were needed due to translational discrepancies.

Doctor questionnaire

The dedicated nurse at each center extracted side effect information from the medical records of enrolled patients after the first and third adjuvant chemotherapy cycle to complete "doctor" questionnaires. These questionnaires were managed exclusively by nurses and were not available to the treating doctors. Furthermore, the nurses managing doctor questionnaires were different to those collecting patient questionnaires at each center.

Statistical methods

Percentages and absolute frequencies of symptom grades were calculated for all symptoms reported in patient and doctor questionnaires. For each symptom, differences in incidence (grade 0 vs grade ≥1) and severity (mean grade) between the first and second set of questionnaires were assessed using McNemar's test and the Wilcoxon signed rank test, respectively. Agreement between patient and doctor side effect reporting (grade 0 *vs.* grade ≥1) was studied on a "per-patient" basis using Cohen's kappa statistic [19]. Both weighted and not weighted Cohen's K statistics were also computed to assess agreement on each grade (grade 0 vs grade 1 vs grade 2 vs grade 3 vs grade 4). The proportion of pairs for which patients and doctors assigned identical grades was computed, along with the proportion of pairs that disagreed by one point for each symptom and the proportion that disagreed by two or more points. Finally, for each symptom the relationship between the number of patients enrolled at each site and the discrepancy in reporting, defined as percentage of

doctor questionnaires where grade was different from that reported by patient, was evaluated using ordinary least square regression. Statistical significance was set at $p<0.05$.

Results

Patient questionnaires after cycles 1 and 3

A total of 604 women (median age 53.4 years, interquartile range (I.Q.R.) 45.0-62.7) were enrolled between January 2011 and October 2013 at 11 Italian sites. The number of patients enrolled at each site varied between 6 and 236 (eTable 1, on-line only). Three patients withdrew consent prior to starting the first cycle of adjuvant chemotherapy. The relevant demographics of the remaining 601 patients are reported in eTable 2 (on-line only). A total of 596 and 581 patient questionnaires were collected after cycles 1 and 3 of adjuvant chemotherapy, respectively. Of these, 594 and 573 had a corresponding questionnaire extracted from the medical charts at the same time point. The median percentage of completed fields was 82% (I.Q.R. 80-88%) for both patient questionnaires. The percentage of fields not filled in for each questionnaire item (i.e., left blank) is shown in eTable3 (online only): the percentage of incomplete fields was very low and did not exceed 6.28% for four of the five fields. However, due to the high percentage of incomplete data on persistence or resolution of symptoms at the time of the visit , variables related to symptom duration were not analyzed here.

The results of the two patient questionnaires are summarized in Table 1 (crosstabulated raw data are shown in eTable 4, online only). There was a reduction in vomiting (severity), diarrhea (both incidence and severity), and pain (both incidence and severity), and a statistically significant increase in dysgeusia (both incidence and severity) and dyspnea (both incidence and severity) in the second patient-completed questionnaire. With respect to doctors' questionnaires (crossutabulated raw data are shown in eTable 5,

online only), only an increase in the incidence (2% vs 4%, p = 0.01) and severity (mean grade 0.3 vs 0.7, p = 0.03) of dyspnea was recorded.

Comparisons between patient and doctor questionnaires

Comparisons between patient and doctor questionnaires after the first chemotherapy cycle are summarized in Table 2 (crosstabulated raw data are shown in eTable 6, online only). The reporting incidence (any grade) was higher in patients than doctors for all side effect items, as was severity (figure 1). Focusing on incidence, patients reported constipation, anorexia, and dysgeusia almost twice as frequently as doctors and fatigue three times more frequently than doctors. Notably, paresthesia and dyspnea were rarely reported by doctors but were reported by 23% and 25% of patients, reaching grade 2 or higher in 4% and 10% of patients, respectively. A similar pattern was observed in data collected after the third cycle of chemotherapy (data not shown). Agreement in toxicity reporting (grade 0 *vs.* grade ≥1) between patients and doctors for each item after the first chemotherapy cycle is summarized in Table 4. For most items except vomiting, agreement was below the definition of "acceptable" (Cohen's kappa statistic <0.40) [20], which was mirrored in the second set of questionnaires (not shown). This low level of agreement could mostly be explained by underreporting by doctors (Table 4). Assessing overall agreement on toxicity grade by both weighted and non-weighted Cohen's K statistics and using multiple imputation to account for missing data provided similar results (eTable 7, online only).

Since the number of patients enrolled at each site varied widely (Table 1s, online only), we sought to assess whether the discrepancies observed between patients and physicians when assessing toxicity (each item, any grade) were associated with the number of patients enrolled. A strong and significant positive association was demonstrated for all ten items included in the questionnaire (Figure 2). Similar results were also observed for the second questionnaire (data not shown).

Discussion

The first aim of this study was to assess whether women undergoing adjuvant chemotherapy for operable breast cancer are able to report and grade ten common subjective side effects using a CTCAE v4.0-derived questionnaire. Secondly, due to the widely recognized problem of underestimating the incidence and severity of chemotherapy-related side effects by doctors, patient-derived information was compared to that extracted from their medical charts.

There was a very high questionnaire response rate (98% and 95% returned a completed questionnaire at each time point), a high proportion of filled-in fields (82% for both the first and second questionnaire), and a low percentage of blank fields with the exception of the question regarding persistence or resolution of toxicity at the time of chemotherapy visit. For this reason, we decided not to analyze the duration of side effects here. However, we are currently analyzing the patient diaries in detail to resolve this issue.

There were significant discrepancies in the reported occurrence and severity of each of the ten items between patients and doctors. Consequently, there was also low agreement in incidence (grade 0 *vs.* grade ≥1) and grading, mainly due to underreporting by doctors. Several other authors have reported a similar phenomenon [5-11]. For example, Di Maio and colleagues recently studied patients enrolled in three prospective clinical trials: one studying elderly patients with breast cancer receiving adjuvant chemotherapy and two studying patients with advanced non-small cell lung carcinoma receiving first-line treatment [9]. The authors compared patient and doctor reporting of six chemotherapy-related side effects (anorexia, nausea, vomiting, constipation, diarrhea, and hair loss) after each of the initial three cycles of chemotherapy. Doctors used CTCAE v2.0, while patients completed PRO questionnaires issued by the European Organization for Research and Treatment of Cancer (EORTC) that included chemotherapy-related side effects rated on a severity scale of “not

at all", " a little", "quite a bit", and "very much". Agreement between doctors and patients was poor, mainly due to doctors underestimating both the incidence and severity of side effects. Notably, kappa values for patient and doctor agreement for the five side effects common to our study (anorexia, nausea, vomiting, constipation and diarrhea) were remarkably similar to those reported here. These findings suggest that poor doctor and patient agreement in side effect reporting is consistent between diverse patient groups (cancer free or metastatic disease), type of treatment received, and management setting (prospective clinical trial or standard treatment).

Our findings also hint at possible reasons for this reproducible phenomenon. First, pairwise comparisons between the two patient questionnaires showed trends toward reduced vomiting, diarrhea, and pain. This suggests that doctors may have correctly identified the side effects and delivered appropriate management, but because vomiting and diarrhea are common, doctors may not have deemed them sufficiently important to report in the charts. Second, there was a statistically significant correlation between discrepancies in side effect reporting and the number of patients enrolled at each institution. Data that we collected during the pre-study surveys provide a possible explanation for this finding (eTable1, online only). With two exceptions, the number of patient accrued corresponded to enrolment commitment, which had to be estimated on the basis of expected number of patients eligible for the study and allocated resources of over a 2-year period. Therefore, we speculate that patient volume and the resources assigned to patient management might be determinants of the discrepancy between doctor and patient reporting of side effects. In particular, when time is constrained, the doctor-patient relationship may focus more on treatment efficacy than on side effects, which might be overlooked or not described or reported in the medical charts. Of note, an Italian study examining separate collection of chemotherapy-related side effect data by doctors and nurses found greater agreement

between patients and nurses than between patients and doctors for most of the items evaluated [8].

Our study suffers from limitations common to similar studies in this area, and a randomized study would be difficult to conduct for methodological reasons. Patients were not involved in the development of the Italian version of the questionnaire, and it is possible that a lack of validation of the comprehension of the statements describing toxicities could be responsible, at least in part, for the observed discrepancies. Doctors at each center were aware of the study but not formally involved. Therefore, they may have consciously or unconsciously focused on the ten side effects considered in this study, thus potentially biasing the discrepancy in side effect reporting. This might have accounted for the lower discrepancy that we observed in centers that enrolled a low number of patients. Indeed, in a prospective study of an 11-item version of the CTCAE distributed to 435 cancer patients and their doctors, there was good agreement between doctors and patients for most side effects [5]. However, for those side effects with a subjective component (e.g., dyspnea, fatigue), agreement tended to be lower despite the involvement of both patients and doctors.

The strengths of this study are that it is large, prospective, and conducted in a homogeneous population of non-metastatic breast cancer patients with exclusion of potential confounders related to baseline cancer symptoms. Most patients were healthy and received anthracycline-based regimens with only minor dose variations at the different participating institutions. Finally, patients received chemotherapy in routine clinical practice and not in a prospective therapeutic trial mandating standardized reporting of side effects by the treating oncologist.

We believe that the approach that we tested in this manuscript offers a number of potential advantages in cancer patients undergoing chemotherapy, in particular those treated in the clinical practice. For example, doctor-patient interaction would benefit from

using a common reference system for reporting and grading toxicity. With the diffusion of electronic medical records and the possibility that patients fill in electronic questionnaires, CTCAE-compliant patient reports could be immediately available to treating doctors. Patients can be reassured that doctors adequately weigh their personal experience with side effects, which my result with better coping and quality of like during treatment. Reconciliation of discrepancies in patient and doctor reports during the visit would improve decision making regarding chemotherapy dosing (i.e. dose delay or dose reduction). This may acquire a particular importance in those high-volume centers, where a constrained doctor-patient relationship may be the cause of underreporting of side effects by doctors.

Conclusions

In summary, this prospective study confirms that breast cancer patients receiving conventional therapy can provide CTCAE-compliant reporting and grading of common side effects related to adjuvant chemotherapy. Similar to other studies, we found that doctors tend to underreport or underestimate side effects. However, although we provide some explanation for this phenomenon, there is currently little direct evidence to explain doctor-related factors, and further studies are warranted [18].

Addressing these open questions is becoming increasingly relevant and, in recognition of the importance of considering direct patient involvement in side effect collection and grading, the National Cancer Institute is financing, supporting, and disseminating a PRO version of the CTCAE system (PRO-CTCAE) [15] based on 78 toxicity items mapped to the CTCAE. For each toxicity, PRO-CTCAE contains up to three patient questions that define the grade of severity. These questions were developed and validated using a methodologically robust process based on cognitive interviewing techniques [21] The English version of PRO-CTCAE is currently being translated into different languages,

including Italian. Our data support the adoption of PRO and highlight the potential of this approach in routine clinical practice.

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Author Conflict of Interest Disclosures

Filippo Montemurro:	no conflict of interest and no financial disclosure
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Access to Data and Data Analysis

Filippo Montemurro, Paola Berchialla and Celeste Cagnazzo had full access to the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Additional information

The results of this paper have been partially presented as a Poster at the 2015 meeting of the American Society of Clinical Oncology.

All the authors of this manuscript have provided substantial contribution in designing the study, recruiting patients, collecting data. All the authors have read and approved the final manuscript draft that was written by the first author (Filippo Montemurro).

References

1. Edwards JE, McQuay HJ, Moore RA, Collins SL. Reporting of adverse effects in clinical trials should be improved: lessons from acute postoperative pain. *J Pain Symptom Manage.* 1999;18(6):427-437.

2. Gwede CK, Johnson DJ, Daniels SS, Trotti A. Assessment of toxicity in cooperative oncology clinical trials: the long and short of it. *J Oncol Manag.* 2002;11(2):15-21.

3. Ioannidis JP, Evans SJ, Gøtzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med.* 2004;141(10):781-788.

4. NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files. http://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed 05/25/2015.

5. Basch E, Iasonos A, McDonough T, et al. Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study. *Lancet Oncol.* 2006;7(11):903-909.

6. Petersen MA, Larsen H, Pedersen L, Sonne N, Groenvold M. Assessing health-related quality of life in palliative care: comparing patient and physician assessments. *Eur J Cancer.* 2006;42(8):1159-1166.

7. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *J Clin Oncol.* 2004;22(17):3485-3490.

8. Cirillo M, Venturini M, Ciccarelli L, Coati F, Bortolami O, Verlato G. Clinician versus nurse symptom reporting using the National Cancer Institute - Common terminology criteria for adverse events during chemotherapy: Results of a comparison based on patient's self-reported questionnaire. *Annals of Oncology.* 2009;20(12):1929-1935.

9. Di Maio M, Gallo C, Leighl NB, et al. Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. *J Clin Oncol.* 2015;33(8):910-915.

10. Gravis G, Marino P, Joly F, et al. Patients' self-assessment versus investigators' evaluation in a phase III trial in non-castrate metastatic prostate cancer (GETUG-AFU 15). *Eur J Cancer.* 2014;50(5):953-962.

11. Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. *J Natl Cancer Inst.* 2011;103(24):1851-1858.

12. Basch E, Jia X, Heller G, et al. Adverse symptom event reporting by patients vs clinicians: Relationships with clinical outcomes. *Journal of the National Cancer Institute.* 2009;101(23):1624-1632.

13. Basch E, Bennett A, Pietanza MC. Use of patient-reported outcomes to improve the predictive accuracy of clinician-reported adverse events. *J Natl Cancer Inst.* 2011;103(24):1808-1810.

14. Bruner DW, Movsas B, Basch E. Capturing the patient perspective: patient-reported outcomes as clinical trial endpoints. *Am Soc Clin Oncol Educ.Book.* 2012:139-144.

15. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst.* 2014;106(9).

16. Reeve BB, Mitchell SA, Dueck AC, et al. Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *J Natl Cancer Inst.* 2014;106(7).

17. Zagadailov E, Fine M, Shields A. Patient-reported outcomes are changing the landscape in oncology care: challenges and opportunities for payers. *Am Health Drug Benefits.* 2013;6(5):264-274.

18. Howell D, Molloy S, Wilkinson K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. *Ann Oncol.* 2015.

19. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas.* 1960;20:10.

20. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb).* 2012;22(3):276-282.

21. Hay JL, Atkinson TM, Reeve BB, et al. Cognitive interviewing of the US national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *Quality of Life Research.* 2014;23(1):257-269.

Figure Legend

Figure 1. Discrepancy in toxicity grading between patients and doctors (first questionnaire)

Figure 2. Correlation between discrepancy in patient and doctors reporting of toxicity grade of each side effect and number of patients enrolled at each center (first questionnaire). Each circle represents a participating Institution. The size of each circle represents the number of patients enrolled in the study.

Table 1. Summary of paired patient questionnaire results

Item*	First Questionnaire % (N)	Second Questionnaire % (N)	Differences between Second and First Questionnaire (95%CI)	P values**
Nausea (550)				
Incidence	69 (379)	73 (402)	4 (0; 8)	0.05
Mean Grade	1.16	1.13	-0.03 (-0.11; 0.05)	0.60
Vomiting (566)				
Incidence	24 (136)	20 (114)	-4 (-8; -1)	0.06
Mean Grade	0.34	0.26	-0.08 (-0.13; -0.02)	0.01
Constipation (554)				
Incidence	52 (298)	49 (271)	-3 (-8; 1)	0.21
Mean Grade	0.68	0.65	-0.03 (-0.10;0.03)	0.43
Anorexia (567)				
Incidence	54 (306)	53 (298)	-1 (-6; 3)	0.56
Mean Grade	0.71	0.68	-0.03 (-0.09;0.04)	0.57
Dysgeusia (537)				
Incidence	51 (276)	58 (314)	7 (2; 12)	<0.01
Mean Grade	0.63	0.73	0.1 (0.04; 0.16)	<0.01
Diarrhea (550)				
Incidence	16 (87)	12 (65)	-4 (-7; -1)	0.02
Mean Grade	0.19	0.14	-0.05 (-0.1; -0.01)	0.03
Fatigue (544)				
Incidence	77 (418)	78 (425)	-1 (-5; 3)	0.58
Mean Grade	1.16	1.15	0.01 (-0.07; 0.08)	0.73
Pain (556)				
Incidence	36 (203)	32 (180)	-4 (-8; 1)	0.08
Mean Grade	0.65	0.54	-0.11 (-0.20; -0.03)	<0.01
Paresthesia (558)				
Incidence	23 (130)	21 (119)	-2 (-6; 2)	0.35
Mean Grade	0.28	0.29	0.01 (-0.05; 0.06)	0.86
Dyspnea (552)				
Incidence	25 (138)	29 (162)	4 (1; 8)	0.03
Mean Grade	0.40	0.47	0.07 (0.001; 0.14)	0.04

Abbreviations: N, number; CI, confidence intervals

*Number in parentheses indicate evaluable pairs of questionnaires for each single item.

**P values for Incidence and Mean Grade were obtained by the McNemar Test with continuity correction and the Wilcoxon signed rank test, respectively. 95%CIs were computed using bootstrap resampling.

Table 2. Summary of paired patient and doctor questionnaires after cycle 1

Item*	Patient Questionnaire % (N)	Doctor Questionnaire % (N)	Differences between Patient and Doctor Questionnaires (95%CI)	P values**
Nausea (539)				
Incidence	67 (360)	40 (216)	27(22;31)	<0.01
Mean Grade	1.10	0.59	0.51 (0.43;0.59)	<0.01
Vomiting (572)				
Incidence	22 (128)	11 (62)	11(9; 14)	<0.01
Mean Grade	0.31	0.16	0.15 (0.11; 020)	<0.01
Constipation (546)				
Incidence	49 (268)	12 (65)	37(33; 41)	<0.01
Mean Grade	0.64	0.15	0.49 (0.42; 0.54)	<0.01
Anorexia (563)				
Incidence	53 (297)	7 (41)	46 (41; 50)	<0.01
Mean Grade	0.69	0.09	0.60 (0.53; 0.66)	<0.01
Dysgeusia (556)				
Incidence	50 (277)	8 (46)	42 (37; 46)	<0.01
Mean Grade	0.61	0.10	0.51 (0.45; 0.57)	<0.01
Diarrhea (567)				
Incidence	14 (81)	4 (25)	10 (7; 13)	<0.01
Mean Grade	0.17	0.06	0.11 (0.07; 0.14)	<0.01
Fatigue (532)				
Incidence	75 (400)	25 (132)	50 (46; 55)	<0.01
Mean Grade	1.11	0.35	0.76 (0.71; 0.79)	<0.01
Pain (517)				
Incidence	32 (165)	10 (52)	22 (18; 26)	<0.01
Mean Grade	0.56	0.15	0.41 (0.33; 0.50)	<0.01
Paresthesia (582)				
Incidence	23 (132)	3 (17)	20 (16; 23)	<0.01
Mean Grade	0.27	0.04	0.23 (0.19; 0.26)	<0.01
Dyspnea (574)				
Incidence	25 (142)	2 (13)	23 (19; 26)	<0.01
Mean Grade	0.39	0.04	0.35 (0.29; 0.41)	<0.01

Abbreviations: N, number; CI, confidence intervals

*Number in parentheses indicate evaluable pairs of questionnaires for each single item.

**P values for Incidence and Mean Grade were obtained by the McNemar Test with continuity correction and the Wilcoxon signed rank test, respectively. 95% CIs were computed using bootstrap resampling.

Table 3. Concordance between patient and doctor questionnaires (missing data excluded) for side effect incidence (yes vs not)

Toxicity	N	Patient yes Doctor yes % (N)	Patient yes Doctor No % (N)	Patient no Doctor yes % (N)	Patient No Doctor No % (N)	κ statistic	95% C.I.
Nausea	539	35 (191)	31 (169)	5 (25)	29 (154)	0.32	0.26-0.39
Vomiting	572	10 (58)	13 (70)	1 (4)	78 (440)	0.54	0.46-0.63
Constipation	546	10 (57)	39 (211)	1 (8)	49 (270)	0.20	0.13-0.24
Anorexia	563	6 (36)	46 (261)	1 (5)	46 (261)	0.10	0.06-0.14
Dysgeusia	556	8 (43)	42 (234)	<1 (1)	50 (276)	0.14	0.10-0.19
Diarrhea	567	4 (21)	11 (60)	1 (4)	85 (482)	0.35	0.24-0.47
Fatigue	532	23 (124)	52 (276)	2 (8)	23 (124)	0.15	0.11-0.19
Pain	517	6 (31)	26 (134)	4 (21)	64 (331)	0.16	0.08-0.23
Paresthesia	582	2 (13)	20 (119)	1 (4)	77 (446)	0.13	0.06-0.20
Dyspnea	574	2 (11)	23 (131)	<12	75 (430)	0.11	0.05-0.17

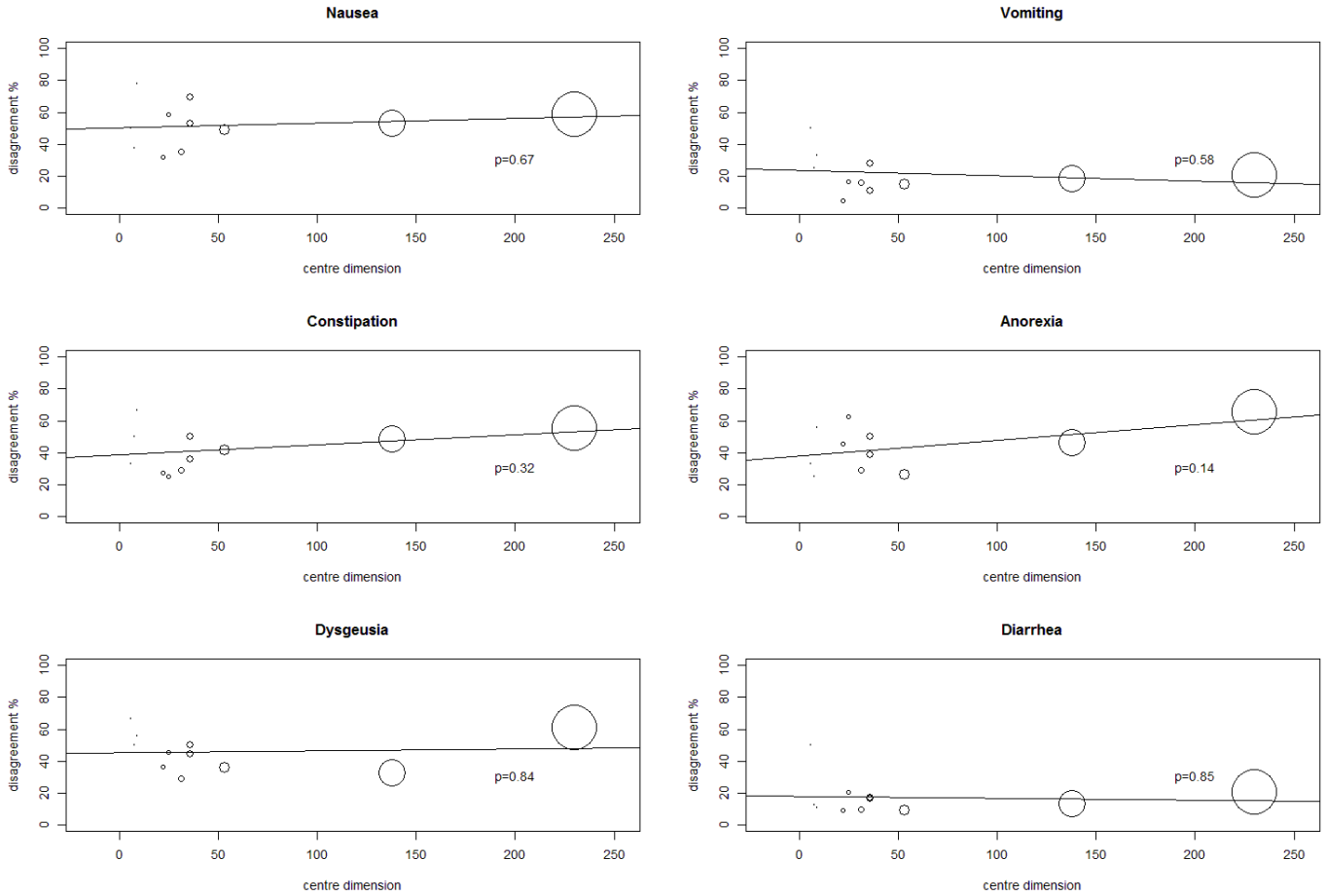

Figure 1. Correlation for the First Questionnaire Between Discrepancy in Patient and Physician Reporting ofAdverse Effect Grade and Number of Patients Enrolled at Each Center