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What is the course of symptoms over time for patients with high initial levels of symptoms and problems?

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Abstract

Purpose

To investigate the mean changes over time in health-related quality of life among advanced cancer patients who did not receive any intervention: changes among all patients versus changes in subgroups of patients with high initial symptom scores.

Methods

Patients with advanced cancer answered two questionnaires, containing the EORTC QLQ-C30 (15 multi- or single-item scales), with approximately one month in between and received no known intervention in the intervening period.

For each QLQ-C30 scale we estimated the mean change among all patients and in subgroups of patients scoring at least 33%, 50% and 66%, respectively, of maximum scale-score in the first questionnaire.

Results

In total, 1,014 patients completed both questionnaires. As hypothesized, we found no change over time in mean scores when including all patients (average mean change=-0.9 (95% CI=-1.5;-0.6)). The subgroups of patients scoring at least 33%, 50% or 66% of maximum scale-score, the score changed towards lower scores with mean changes of -9.2 (95% CI=-10.1;-8.4), -13.1 (95% CI=-14.4;-11.8), and -15.6 (95% CI=-17.2;-13.9), respectively.

Conclusions

We quantified the magnitude of change over a one month period in health-related quality of life in stable advanced cancer patients, and in sub-groups selected according to specific, initial symptom levels. This information may help the interpretation of longitudinal studies of patients selected via screening.

Introduction

Identifying patients who have symptoms and problems and who are therefore considered in need for additional service may enable appropriate referral and maximize effective utilization of e.g., psychosocial services, a view that is supported by clinical practice guidelines [1]. For example in trials of psychosocial interventions in cancer patients, studies have found that the largest improvements in psychological distress, cognitive impairment and quality of life can be expected among patients with high initial levels of distress [2].

Therefore, quite sensibly, trials investigating the effect of a psychosocial intervention may often wish to preselect patients, who the researchers believe may benefit from the intervention. Generally, a target population is first determined and then individuals with a level of distress above a certain threshold within that population are included. However, one might assume that when screening patients, and thereby grouping individuals according to their initial high level of distress, the patients may reach a more average level over time – even without an intervention. This may be because those with high initial distress have a greater opportunity to improve than individuals with less extreme scores. It may also be because symptoms and problems have a tendency to pass, because patients will seek treatment outside the intervention investigated due to their distress, or the high score may be an error, e.g., if the patient has selected the wrong response option.

We could think of this potential change among patients with high initial scores as a regression towards the mean (RTM), although this is not the standard use of the term. RTM is the tendency for a variable that is extreme on its first measurement will tend to be closer to the average on its second measurement – and an observation that is extreme on its second measurement will tend to have been closer to the average on its first [3].

To our knowledge, no papers have investigated the mean changes in symptoms and problems over time in advanced cancer patients with higher initial scores who did not receive an intervention. The purpose of this paper was therefore to empirically investigate this mean change over time (which could be thought of as a potential RTM) for subgroups of patients with different levels of levels of distress at first assessment.

Our hypotheses were:

- 1) The correlations between repeated measurements of symptoms or problems with a month in between are moderate to high when including all patients in the sample, indicating relatively minimal change in the measurements within subjects.
- 2) The average level of symptoms and problems in a cross-sectional sample of cancer patients NOT receiving any intervention is not different one month later, indicating no mean change.
- 3) There are substantial mean changes over time when including only patients having high initial scores.

Method

Patients

The inclusion of patients has been described previously [3-4]. To achieve a random and representative sample we included patients from three out of 14 hospital regions across Denmark. From each participating department a random sample of cancer patients (selected based on date of birth) was included if patients: a) were at least 18 years, b) lived in the region, c) had been in contact with the hospital department within the previous year, d) had cancer (solid tumors or lymphomas stages 3 or 4 according to the TNM system[6]; cancer in the central nervous system and small cell lung cancer in any stage, or leukemia, e) spoke Danish, and f) did not have a cognitive impairment or a psychiatric co-morbidity. Eligible patients received a questionnaire and a letter including informed consent by mail. The study was approved by the local ethics committee (01-116/03 and 11-143/03) and took place from October 2004 to January 2006.

Design and intervention

Patients received the first questionnaire at a random time that was not affected by their treatment status or their contact to the hospital. Approximately two weeks after the first questionnaire was received by the research coordinator, an additional questionnaire was sent to the patients. Between the first and the second questionnaire no intervention was initiated based on the study. Thus, we expected the same level of distress in the two assessments, as the patients were contacted at a random time unrelated to their treatment.

Questionnaires

The EORTC QLQ-C30 [6-7] was administered at both occasions. It assesses health-related quality of life and consists of nine multi-item scales measuring: physical function, role function, emotional function, cognitive function, social functioning, global health status/quality of life, fatigue, nausea and vomiting, and pain, and six single-item scales: dyspnoea, insomnia, lack of appetite, constipation, diarrhoea and financial difficulties. For symptoms scales a high score indicate more symptom (the higher the worse). For function scales a high score represent better functioning (the higher the better).

Statistical analyses

The data were analysed with SAS statistical software, version 9.4 [7].

The answers to the EORTC QLQ-C30 were converted to 0-100 scales according to the scoring manual [6-7].

We estimated the intraclass correlation between the first and second questionnaire for each of the 15 scales in the EORTC QLQ-C30 using the total sample. The interclass correlations coefficient is equivalent to the quadratic weighted kappa and a coefficient of 1 indicates maximum possible correlation, whereas a coefficient of 0 indicates no correlation [10].

We calculated the mean change over time for each of the 15 scales in the EORTC QLQ-C30. First, we did this including all patients who had answered the two questionnaires in order to test hypothesis 1. Second, we investigated the mean change for patients who had scored at least 33%, 50% or 66%, respectively, of what corresponds to “maximum distress score” (for a symptom scale this corresponds to a score of 100, for a function scale and Global health status/QoL this corresponds to a score of 0) in the first questionnaire. A score of 33% corresponds to an average response of “a little” (symptom/problem) to the items in a scale, 50% is in the middle of the scale and 66% corresponds to “quite a bit” symptom/problem.

Results

Participants

The first questionnaire was completed by 1,447 patients and 1,014 of these also completed the second questionnaire with a mean of 31 days in between (SD=15.5 days). Table 1 shows the baseline characteristics of the 1,014 patients who completed both questionnaires.

(Table 1 approximately here)

As hypothesized, when including all patients there was a moderate to high correlation between the first and second measurements of the 15 scales ranging from 0.55 (95% CI=0.48;0.62) to 0.89 (95% CI= 0.87;0.91) (table 2).

(Table 2 approximately here)

As hypothesized, there were very small changes over time in the 15 scales ranging from -1.9 to 2.1; the mean change across scales was -1.0 (95% CI=-1.5;-0.6) (Table 3).

The mean change for increasing cut-off values is shown in Table 3. As hypothesized, there were substantial changes over time in patients with high initial scores. The mean change across all scales increased with higher cut-off threshold for initial scores from mean -9.2 (95% CI=-10.1;-8.4) for cut-off at least 33% to -15.6 (95% CI=-17.2;-13.9) for cut-off at least 66% of maximum score.

(Table 3 approximately here)

The largest change was observed for nausea/vomiting: -20.3 (95% CI=-24.9;-15.7), -29.4 (95% CI=-37.3;-21.5) and -37.9 (95% CI=-49.2;-26.7), for patients scoring at least 33%, 50% or 66% of maximum initial score (table 3), respectively. Figure 1 shows the distribution of scores for nausea/vomiting at the two assessments among patients scoring at least 33% of maximum score in the first questionnaire. Obviously, there are therefore no observations below 33 at the first assessment, and the histogram exemplifies how the level of symptoms is more evenly distributed at the second measurement.

(Figure 1 approximately here)

Among functional scales the largest change was for social functioning: 12.6 (95% CI=10.2;15.0), 17.7 (95% CI=14.4;20.9) and 19.8 (95% CI=15.6;24.0) for patients initially scoring 33%, 50% or 66% of maximum distress, respectively.

Discussion

The present study provides data supporting our three hypotheses of (1) moderate to high correlations between the first and second assessment of symptoms and problems, (2) no mean change over time in the total sample of advanced cancer patients, and (3) substantial changes over time in patients having high initial scores with larger changes for higher cut-points. We used data for change over time in the 15 scales of the EORTC QLQ-C30 from a large sample of presumably stable cancer patients. To the best of our knowledge this is the first study to empirically investigate the change over time in symptoms and problems, according to various cut-points, in advanced cancer patients, who did not receive an intervention.

Our findings showed moderate to high correlations between the first and second measurements of symptom and problems and very small changes over time when including all patients in the analysis. This confirmed that, overall, patients were stable. However, when selecting patients with initial high levels of distress we found large mean changes. The largest change was found for nausea/vomiting with mean changes of -20.3 to -37.9.

These findings can be interpreted as the hypothesised regression toward the mean (RTM). RTM has previously been reported in studies measuring blood pressure and cholesterol, where any two observations are rarely identical and higher initial values are likely to be followed by an observation closer to the person's average value [9,10, 11].

We believe that the mean changes found in this study cannot exclusively be viewed as a result of RTM in its traditional meaning, but could also be caused by a variety of reasons including placebo effects, patients seeking treatment on their own initiative, or patients simply getting accustomed to the distress. This illustrates that if patients with high initial scores are offered intervention, it may be

difficult to distinguish a treatment effect from changes in symptoms and problems caused by other reasons than the intervention.

A limitation of the study could be the missing data. Not all patients filled in the second questionnaire. It is possible that the patients who had the worst symptoms and problems at the second measurement did not answer the second questionnaire and this may bias the results. However, results are still applicable to the interpretation of other questionnaire studies where the same attrition is likely to occur.

In conclusion, this study has produced estimates of the magnitude of mean changes for advanced cancer patients when subgroups having high initial scores are followed over a period of approximately one month. The findings contribute to the understanding of the dynamic nature of symptoms and problems, which is essential when interpreting results from clinical studies. Failure to acknowledge a mean change occurring as a result of preselecting patients with initially high levels of distress may lead to wrong conclusions if changes over time are solely interpreted as effects of intervention.

Acknowledgement

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Conflict of interests

The authors declare that they have no academic or financial conflicts of interests.

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Table 1. Characteristics of the 1014 participants who had answered both questionnaires.

Characteristics		N	%
No. of patients		1014	
Age, mean (SD)		62(13)	
Gender	Male	466	56
	Female	548	54
Primary tumour site	Lung	58	6
	Head and neck	50	5
	Gynecological	74	7
	Prostate	68	7
	Breast	166	16
	Gastrointestinal	158	16
	Bladder	25	2
	Multiple myeloma	37	4
	Chronic myelogenous leukemia	24	2
	Chronic lymphocytic leukemia	85	8
	Acute myeloid leukemia	27	7
	Other	101	10
Cancer stage	Stage 3	343	34
	Stage 4	313	31
	Haematological	327	32
	Not applicable	31	3
Diagnosis received	0-6 months	121	13
	6-12 months	130	14
	1-2 years	185	19
	2-5 years	168	18
	5-10 years	90	10
	>10 years	247	26
	Missing	73	
Contact type	Hospitalized	106	11
	Out-patient	897	89
	Missing	8	
Department	Surgical	315	31
	Oncological	339	34
	Medical	75	7
	Haematological	285	28

Table 2. Mean EORTC QLQ-C30 scale scores for the first and second measurements (with a mean of 31 days in between) and their correlations and their 95% confidence intervals.

Symptom/problem	N	First measurement mean [95 % CI]	Second measurement mean [95 % CI]	Correlation	95 % CI
Role function	985	68.9 [67.2;70.8]	61.1 [69.4.2;72.8]	0.79	0.76;0.82
Physical function	996	77.1 [75.9;78.3]	77.1 [75.9;78.3]	0.89	0.87;0.91
Emotional function	963	80.3 [79.2;81.5]	80.1 [79.7;81.9]	0.78	0.75;0.81
Social function	962	81.4 [80.1;82.8]	83.5 [82.1;84.8]	0.69	0.64;0.74
Cognitive function	967	81.8 [80.6;83.0]	82.4 [81.2;83.6]	0.78	0.78;0.82
Fatigue	994	34.7 [34.2;37.2]	33.8 [32.4;35.3]	0.82	0.79;0.84
Pain	1006	23.1 [21.6;24.6]	22.4 [20.9;23.9]	0.73	0.69;0.78
Nausea and vomiting	993	7.1 [6.2;7.9]	6.5 [5.7;7.4]	0.54	0.45;0.62
Appetite loss	992	14.4 [12.9;15.8]	13.0 [11.7;14.4]	0.67	0.61;0.73
Constipation	959	10.5 [9.3;11.7]	10.4 [9.3;11.6]	0.67	0.61;0.74
Dyspnea	983	17.6 [16.2;19.0]	16.3 [14.9;17.7]	0.72	0.67;0.77
Diarrhoea	961	12.2 [11.0;13.4]	12.0 [10.8;13.2]	0.55	0.48;0.62
Financial problems	959	10.4 [9.1;11.6]	9.7 [8.5;10.9]	0.70	0.64;0.76
Insomnia	991	23.3 [21.8;24.9]	21.5 [20.1;23.0]	0.71	0.66;0.75
Global health status/QoL	964	67.9 [66.6;69.2]	67.6 [66.3;68.9]	0.73	0.69;0.76

All scores range from 0-100. In function scales (role function, physical function, emotional function, social function and cognitive function) and Global health status/QoL a high score indicate better function. In symptom scales (fatigue, pain, nausea and vomiting, appetite loss, constipation, dyspnea, diarrhoea, financial problems and insomnia) a high score indicates more symptom.

Table 3. Mean difference in QLQ-C30 scales measured with a mean of 31 days in between for patients scoring at least what corresponds to 33%, 50% and 67% of maximum distress, respectively, in the first questionnaire and all patients.

Symptom/problem	All patients		Cut-off on 33%		Cut-off on 50%		Cut-off on 66%	
	N	Mean change ^a [95 % CI]	N	Mean change ^a [95 % CI]	N	Mean change ^a [95 % CI]	N	Mean change ^a [95 % CI]
Role function	985	2.1 [0.9;3.2]	486	8.7 [6.8;10.5]	314	13.1 [10.7;15.5]	233	14.6 [11.8;17.4]
Physical function	985	0.0 [-0.5;0.6]	315	2.7 [1.3;3.9]	149	4.9 [2.8;6.9]	70	5.9 [8.6;17.6]
Emotional function	963	0.5 [-0.3;1.3]	273	7.1 [5.2;9.0]	127	11.3 [8.4;14.2]	57	13.1 [8.6;17.6]
Social function	962	2.0 [0.9;3.1]	299	12.6 [10.2;15.0]	170	17.7 [14.4;20.9]	96	19.8 [15.6;24.0]
Cognitive function	967	0.6 [-0.2;1.3]	285	7.7 [5.8;9.6]	134	10.9 [7.8;14.1]	75	11.1 [6.9;15.3]
Fatigue	994	-1.9 [-2.8;-0.9]	551	-5.9 [-7.3;-4.6]	291	-9.6 [-11.6;-7.6]	210	-16.8 [-13.4;-8.6]
Pain	1006	-0.6 [-1.7;0.5]	369	-10.3 [-12.4;-8.1]	238	-14.6 [-17.3;-11.9]	154	-16.8 [-20.3;-13.2]
Nausea and vomiting	993	-0.5 [-1.4;0.3]	106	-20.3 [-24.9;-15.7]	51	-29.4 [-37.3;-21.5]	29	-37.9 [-49.2;-26.7]
Appetite loss	992	-1.4 [-2.5;-0.3]	259	-16.4 [-19.7;-13.3]	124	-25.0 [-30.3;-19.7]	124	-25.0 [-30.3;-19.7]
Constipation	959	-0.0 [-1.0;0.9]	211	-12.2 [-15.3;-8.9]	68	-21.1 [-27.9;14.2]	68	-21.1 [-27.9;-14.2]
Dyspnea	983	-1.3 [-2.3;-0.3]	360	-10.6 [-12.8;-8.5]	123	-20.1 [-24.1;-15.9]	123	-20.9 [-24.1;-15.9]
Diarrhoea	961	-0.2 [-1.4;0.9]	260	-15.8 [-18.5;-13.1]	75	-24.4 [-30.4;-18.5]	75	-24.4 [-30.3;-18.5]
Financial problems	959	-0.6 [-1.6;0.3]	191	-15.8 [-19.0;-12.4]	78	-20.9 [-27.0;-14.9]	78	-20.9 [-27.0;-14.9]
Insomnia	991	-1.8 [-2.9;-0.6]	463	-11.1 [-13.1;9.1]	167	-19.2 [-22.8;-15.5]	167	-19.2 [-22.8;-15.5]
QoL	964	-0.3 [-0.2;0.7]	490	4.1 [2.6;5.6]	287	8.7 [6.7;10.6]	126	16.7 [13.8;19.7]
Average mean change ^b	1008	-0.9 [-1.5;-0.6]	838	-9.2 [-10.1;-8.4]	561	-13.1 [-14.4;-11.8]	474	-15.6 [-17.2;-13.9]

All scores range from 0-100. In function scales (role function, physical function, emotional function, social function and cognitive function) and QoL a high score indicate better function. In symptom scales (fatigue, pain, nausea and vomiting, appetite loss, constipation, dyspnea, diarrhoea, financial problems and insomnia) a high score indicates more symptom.

^a Calculated as mean difference between scores measured with the first questionnaire and the second questionnaire. A positive difference in the function scales indicates better function at the second measurement. A negative difference in the symptom scales indicates less symptom at the second measurement.

^b The average mean change was calculated as the sum of mean changes in all scales. All changes in the average mean was calculated as positive, e.g. high scores indicates more symptom/problem.

Figure 1. Nausea/vomiting scores as measured by the first and second questionnaire for patients scoring at least 33 in the first questionnaire. Scores range from 0-100 with a high score indicating a high level of nausea/vomiting.

