Pergamon

European Journal of Cancer Vol. 30A, No. 5, pp. 635–642, 1994

0959–8049/94 $7.00 + 0.00

0959-8049(93)E0050-E

The EORTC QLQ-LC13: a Modular Supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for Use in Lung Cancer Clinical Trials

B. Bergman, N.K. Aaronson, S. Ahmedzai, S. Kaasa and M. Sullivan for the EORTC Study Group on Quality of Life

The EORTC Study Group on Quality of Life has developed a modular system for assessing the quality of life of cancer patients in clinical trials composed of two basic elements: (1) a core quality of life questionnaire, the EORTC QLQ-C30, covering general aspects of health-related quality of life, and (2) additional disease- or treatment-specific questionnaire modules. Two international field studies were carried out to evaluate the practicality, reliability and validity of the core questionnaire, supplemented by a 13-item lung cancer-specific questionnaire module, the EORTC QLQ-LC13. In this paper, the results of an evaluation of the QLQ-LC13 are reported. The lung cancer questionnaire module comprises both multi-item and single-item measures of lung cancer-associated symptoms (i.e. coughing, haemoptysis, dyspnoea and pain) and side-effects from conventional chemo- and radiotherapy (i.e. hair loss, neuropathy, sore mouth and dysphagia). It was administered to patients with non-resectable lung cancer recruited from 17 countries. In total, 883 and 735 patients, respectively, completed the questionnaire prior to and once during treatment. The symptom measures discriminated clearly between patients differing in performance status. All item scores changed significantly in the expected direction (i.e. lung cancer symptoms decreased and treatment toxicities increased) during treatment. With one exception (problems with a sore mouth), the change of toxicity measures over time was related specifically to either chemo- or radiotherapy. However, the single item on neuropathy did not measure adequately the full range of symptoms. The hypothesised scale structure of the questionnaire was partially supported by the data. The multi-item dyspnoea scale met the minimal standards for reliability (Cronbach α coefficient >0.70), while the pain items did not form a scale with reliability estimates acceptable for group comparisons. In conclusion, the results from international field testing lend support to the EORTC QLQ-LC13 as a clinically valid and useful tool for assessing disease- and treatment-specific symptoms in lung cancer patients participating in clinical trials, when combined with the EORTC core quality of life questionnaire. In a few areas, however, the questionnaire module could benefit from further refinements. In addition, its performance over a longer period of time still needs to be investigated.

Key words: lung cancer, quality of life, chemotherapy, radiotherapy
Eur J Cancer, Vol. 30A, No. 5, pp. 635–642, 1994

INTRODUCTION

IN 1986, the European Organisation for Research and Treatment of Cancer (EORTC) Study Group on Quality of Life initiated a research programme (EORTC protocol 15861) with the long-term goal of developing an integrated measurement system for evaluating the quality of life of cancer patients participating in clinical trials [1]. A modular assessment approach was adopted to reconcile the requirements of generalisability of results across studies and sensitivity to specific research questions. A multi-dimensional core questionnaire was generated to cover basic quality of life domains, including physical, emotional and social functioning and global quality of life. Additional disease- and treatment-specific questionnaire modules would be developed to complement the core questionnaire.

The methodological considerations involved in constructing the core questionnaire and interim results of the research programme have been discussed in detail elsewhere [2, 3]. Briefly, when employed in a large scale international field study, a first generation 36-item core questionnaire, the EORTC QLQ-C36, showed satisfactory psychometric properties, as well as cross-cultural validity, but the results also pointed to some areas in which the questionnaire could benefit from further development [3]. A refined 30-item version of the questionnaire, the EORTC QLQ-C30, was subsequently submitted to field testing in a similar cross-cultural context. The results of this evaluation lent support to the QLQ-C30 as a reliable and valid research tool for assessing the quality of life of cancer patients in international clinical trials [4].

While the long-term objective was to develop an instrument with applicability across a broad range of cancer diagnoses, it was considered appropriate to initially employ a more homogeneous patient sample for field testing of the questionnaire. Patients

Table 1. Patient recruitment by country

Country	Number of patients	
	Study 1	Study 2
Australia	52	24
Austria	18	—
Belgium	62	25
Canada	57	58
Denmark	13	11
Germany	53	35
France	31	17
Great Britain	21	41
Italy	17	14
Japan	47	—
The Netherlands	24	30
Norway	39	36
Spain	48	—
Sweden	39	31
Switzerland	4	—
United States	—	24
Yugoslavia	12	—
Total	537	346

with non-resectable lung cancer receiving chemotherapy or radiotherapy were selected as the initial target population for study. This choice was based on the high incidence and relatively rapid progression of the disease, facilitating both patient accrual and evaluation of responsiveness of the questionnaire to change in health status over time. To address specific symptoms associated with lung cancer and its treatment, which were either not incorporated or covered only in general terms by the core questionnaire, a complementary lung cancer-specific questionnaire module was developed and administered together with the core questionnaire. In this paper, we report on the data relating to this lung cancer-specific questionnaire module.

PATIENTS AND METHODS

Over two time periods (1987–1989 and 1990–1991), consecutive samples of patients with lung cancer were recruited from participating institutions in Europe, North America, Australia and Japan (Table 1). In both studies (subsequently referred to as studies 1 and 2, respectively) the eligibility criteria were newly diagnosed and non-resectable lung cancer, treatment involving either chemo- or radiotherapy and informed consent. No restrictions were employed with regard to age, performance status, histological type or stage of disease. Performance status was measured by the ECOG scale [5].

Correspondence to B. Bergman at the Department of Pulmonary Medicine, Renströmska Hospital, P.O. Box 17301, S-402 64 Göteborg, Sweden.
N.K. Aaronson is at the Netherlands Cancer Institute, Amsterdam, the Netherlands; S. Ahmedzai is at the Leicestershire Hospice, Leicester, U.K.; S. Kaasa is at Trondheim University Hospital, Trondheim, Norway; and M. Sullivan is at the Sahlgrenska Hospital, Göteborg, Sweden.

Received 23 Aug. 1992; accepted 6 Dec. 1993.

Baseline clinical characteristics of the patient samples are displayed in Table 2. Approximately two-thirds of all patients had a performance status better than 2, i.e. they were fully ambulatory. Metastatic disease was reported in approximately one-third of all patients. In both studies, less than 20% of patients had weight loss exceeding 10% of total body weight. The patients ranged in age between 30 and 87 years (mean 62 years) in study 1, and between 35 and 89 years (mean 63 years) in study 2. Twenty-one and twenty-four per cent, respectively, were female.

The patients were requested to fill in the core quality of life questionnaire (the QLQ-C36 or the QLQ-C30), complemented by a 13-item lung cancer-specific questionnaire module, the QLQ-LC13, at two points in time: (1) prior to the start of treatment ('pretreatment'); and (2) following the first course of radiotherapy or the second course of chemotherapy ('on-treatment'). The time interval between pre- and on-treatment administrations was chosen to facilitate detection of both clinical changes and treatment toxicities, while minimising sample attrition due to severe illness or death. In addition to the questionnaire assessment, treatment toxicities were rated by the treating physicians, employing selective items of the WHO Acute and Subacute Toxicity Scale [6].

The content areas covered by the core questionnaire are summarised in Table 3. Detailed results of the testing and analyses of the QLQ-C36 and QLQ-C30 have been reported elsewhere [3, 4]. Data relating to the core questionnaire were used selectively for evaluation of the lung cancer questionnaire module.

The following criteria guided the construction of the lung cancer-specific questionnaire module:

(1) It should be comprised of items that are specific to lung cancer and its standard treatment, and that are insufficiently covered by the core questionnaire.
(2) It should have the same format and employ the same time frame as the core questionnaire.
(3) It should be reliable, valid and responsive to clinical status and change over time.

Given this framework, 13 items with potential impact on the patients' well-being during treatment were selected and adopted

Table 2. Pretreatment clinical characteristics of study sample

	Study 1 (n = 537) (%)	Study 2 (n = 346) (%)
Tumour type		
Non-small cell lung	62	62
Small cell lung	38	38
Disease stage		
Local	26	20
Loco-regional	33	49
Metastatic	41	31
ECOG performance status		
0–1	66	69
2–4	34	31
Weight loss		
None	44	49
≤10%	37	35
>10%	19	16

Table 3. Content areas covered by the EORTC core quality of life questionnaire

	No. of items	
	QLQ-C36 (Study 1)	QLQ-C30* (Study 2)
Physical functioning	7	5
Role functioning	2	2
Emotional functioning	8	4
Cognitive functioning	1	2
Social functioning	2	2
Global quality of life	2	2
Fatigue	5	3
Nausea and vomiting	2	2
Pain	1	2
Dyspnoea	1	1
Sleep disturbance	1	1
Appetite loss	1	1
Constipation	1	1
Diarrhoea	1	1
Financial impact	1	1

* QLQ-C30 is the current version of the core questionnaire.

for the lung cancer questionnaire module by the project group. The content of the QLQ-LC13 is presented in Table 4. With the exception of dyspnoea and pain, lung cancer-related symptoms and treatment side-effects are covered by single items. All items employ a 1-week time frame. With the exception of the first item on pain medication, which has dichotomous response categories (no or yes), all items are scored on a 4-point categorical scale ranging from 1 (not at all) to 4 (very much). For ease of presentation and interpretation, all scale and item scores are linearly transformed to a 0 to 100 scale, with higher scores representing increasing symptom levels.

Statistics

A range of tests were performed to assess the psychometric properties (i.e. reliability and validity) of the QLQ-LC13, and its contribution to explaining the variance in patients' ratings of global quality of life.

Table 4. Content of the EORTC lung cancer questionnaire module

1.	How much did you cough?
2.	Did you cough blood?
3.	Were you short of breath when you rested?
4.	Were you short of breath when you walked?
5.	Were you short of breath when you climbed stairs?
6.	Have you had a sore mouth or tongue?
7.	Have you had trouble swallowing?
8.	Have you had tingling hands or feet?
9.	Have you had hair loss?*
10.	Have you had pain in your chest?
11.	Have you had pain in your arm or shoulder?
12.	Have you had pain in other parts of your body? If yes, where?
13.	Did you take any medicine for pain? If yes, how much did it help?

* In study 1, the wording of this item was: "Have you been bothered by hair loss?"

Likert's method of summated ratings [7] was employed to test whether individual questionnaire items could be aggregated into multi-item scales. When appropriate, the mean score of a set of items hypothesised to form a scale was calculated, yielding a total score based on the original metric of the individual item responses. The reliability (i.e. internal consistency) of the multi-item scales was assessed by Cronbach's α coefficient [8]. Internal consistency estimates of a magnitude ≥ 0.70 were considered acceptable for group comparisons.

The validity of the questionnaire was estimated in several ways. Clinical validity was evaluated by the method of known-groups comparison [9]. This method allows one to examine the degree to which the questionnaire is able to distinguish between subgroups of patients formed on the basis of clinical measures, including ECOG performance status, stage of disease, WHO toxicity ratings and treatment modality. Factorial analysis of variance (ANOVA) was employed to test for statistical significance of group differences.

Change in QLQ-LC13 scores over time was calculated and tested for statistical significance by means of repeated measures analysis of variance.

The responsiveness of the questionnaire to changes in health status over time was also evaluated. While there is no 'objective' clinical measure of global health status, performance status was considered as a reasonable substitute for such a measure. Repeated measures ANOVA was used to test for the statistical significance of QLQ-LC13 score changes as a function of observed changes in performance status. Similarly, QLQ-LC13 toxicity score changes were analysed as a function of treatment modality. In addition, correlation analysis was used for comparison of on-treatment QLQ-LC13 toxicity ratings with corresponding WHO toxicity ratings provided by the physicians.

Finally, the relative contribution of various disease- and treatment-related symptoms, as measured by the QLQ-LC13, towards explaining the variance in global quality of life ratings derived from the core questionnaire was examined by a stepwise multiple regression analysis.

RESULTS

Pretreatment assessment

Descriptive statistics for the pretreatment QLQ-LC13 disease-related items are presented in Table 5. Substantial coughing was reported by approximately 40% of all patients, while haemoptysis was reported infrequently. The three dyspnoea items represent increasing levels of exertion, which is clearly reflected in the results. Low mean scores were reported on dyspnoea at rest, moderate mean scores on walking dyspnoea, and the highest mean scores on dyspnoea while climbing stairs. Approximately 20% of the patients reported substantial pain in either the chest, the arm and shoulder, or in other parts of the body. Approximately half of the patients were taking pain medication. Of these, approximately one-third reported no or little pain relief. As expected, the mean pretreatment QLQ-LC13 scores on treatment side-effects (not in Table 5), were low, ranging from 3.6 (hair loss, study 2) to 12.5 (trouble with swallowing, study 1). The distribution of questionnaire item responses was highly consistent across the two studies.

Multi-item scales. Two sets of items (on dyspnoea and pain, respectively) in the QLQ-LC13 questionnaire were hypothesised to form multi-item scales. Additionally, the core questionnaire (both the QLQ-C36 and the QLQ-C30) included at least one additional item on these symptoms. These core questionnaire items were also included in the scale analysis.

Table 5. Descriptive statistics for the QLQ-LC13 pretreatment symptom scores

Symptom	Study 1 (n = 537)			Study 2 (n = 346)		
	Mean*	S.D.	%pos†	Mean*	S.D.	%pos†
Coughing	46.2	28.7	39	44.3	30.0	39
Haemoptysis	10.2	20.0	5	8.7	19.3	5
Dyspnoea						
Resting	17.2	26.3	14	16.2	26.3	12
Walking	34.5	32.6	30	35.5	31.2	30
Climbing stairs	50.0	35.2	47	50.9	34.0	51
Pain						
Chest	26.9	29.8	21	25.5	30.8	19
Arm/shoulder	20.3	30.2	18	20.1	29.1	16
Other sites	22.1	31.9	21	20.6	30.6	19
Medicine intake‡			48			54
Medicine effect§			38			31

* Scores range from 0 to 100. Higher scores indicate more complaints. † Percentage of patients responding "quite a bit" or "very much". ‡ Percentage of patients taking pain medication. § Percentage of patients taking medication with no or little pain relief.

Descriptive statistics and reliability coefficients for the hypothesised scales are displayed in Table 6. The QLQ-LC13 dyspnoea items formed a three-item scale with internal consistency estimates clearly exceeding the minimum levels required for group comparisons. When combined with the core questionnaire item on dyspnoea, the reliability of the four-item scale was improved further, with Cronbach's α coefficients averaging 0.85 in both studies.

In contrast, the QLQ-LC13 pain items did not form a reliable scale. When combined with the core questionnaire item(s) on pain, the α coefficient improved considerably, indicating that the QLQ-LC13 pain items correlated better with the general pain item(s) in the core questionnaire than with each other. However, in study 2, the reliability of the combined five-item pain scale was inferior to that of the two-item core questionnaire scale alone.

Consistent with the results of the scale analysis, the dyspnoea items were aggregated into a four-item scale (including also the single dyspnoea item in the core questionnaire). This scale was used for further analysis of validity and time-dependent changes. Conversely, the QLQ-LC13 pain items were not aggregated but rather were employed as single items in the corresponding analyses.

Variance by disease stage. In order to evaluate the clinical validity of the QLQ-LC13 symptom measures, an analysis of variance by disease stage and level of performance status was performed. The mean pretreatment symptom scores by disease stage are displayed in Figure 1 (merged data from studies 1 and 2). As expected, patients with metastatic disease reported higher levels of pain as compared with patients with local disease. Similarly, patients with metastatic disease reported more frequent use of pain medication ($P < 0.001$, not in Figure 1).

However, these results, based on the analysis of the total patient population, were not entirely consistent across the two studies. In study 1, there was no clear relationship observed between disease stage and chest pain ($P > 0.05$) while in study 2 no significant effect of disease stage on ratings of extrathoracic

Table 6. Descriptive statistics and reliability estimates of hypothesised multi-item scales in the pretreatment QLQ-LC13 questionnaire

Content area, source	No. of items	Scale properties					
		Study 1			Study 2		
		Mean	S.D.	α	Mean	S.D.	α
Dyspnoea							
QLQ-LC13	3	33.9	27.2	0.83	34.0	25.6	0.81
QLQ-LC13 + C36/30	4	36.0	26.6	0.86	36.2	25.2	0.85
Pain							
QLQ-LC13	3*	23.0	22.0	0.53	21.7	21.7	0.54
QLQ-LC13 + C36	4	25.6	23.0	0.71		—	
QLQ-LC13 + C30	5		—		25.0	23.7	0.80
QLQ-C30†	2		—		29.9	31.3	0.83

* The item on pain medication was excluded due to its response format. † Two-item pain scale from the core questionnaire, for comparison.

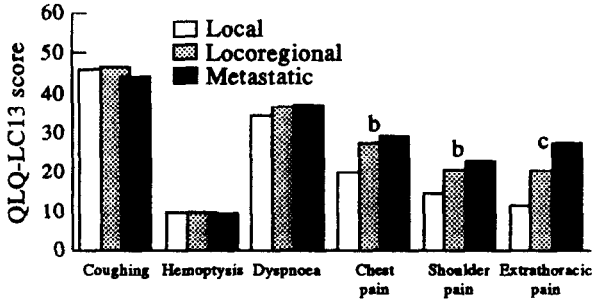

Figure 1. Pretreatment QLQ-LC13 symptom scores (merged data from studies 1 and 2) by stage of disease. The levels of statistical significance are indicated with a ($P < 0.05$), b ($P < 0.01$), or c ($P < 0.001$); factorial analysis of variance.

pain was found ($P > 0.1$). In neither of the two studies was stage of disease related significantly to patients' self-reported coughing, haemoptysis or dyspnoea.

Variance by performance status. The relationship between pretreatment performance status and QLQ-LC13 symptom scores is shown in Figure 2. In contrast to stage of disease, performance status, recoded into two levels (0–1 versus 2–4), was related significantly to pretreatment dyspnoea, with elevated symptom score levels found primarily in patients with a poorer performance status. This finding was consistent across both studies.

Statistically significant differences in pain scores were also observed as a function of performance status (Figure 2), although the results were not entirely consistent across the two studies. In study 1, the scores on arm/shoulder pain did not vary significantly by performance status ($P > 0.1$), while in study 2, extrathoracic pain was not related significantly to performance status ($P > 0.05$). Both coughing and haemoptysis were significantly more pronounced in the poor performance status group.

While the intake of pain medication was associated significantly with both disease stage and performance status, the perceived effect of pain medication was unrelated to either of these clinical variables. To explore this latter finding further, a separate analysis of medication effect was performed, employing a core questionnaire item on general pain as a reference measure. Contrary to expectations, a high percentage (approximately 75%) of the patients who reported no help from their medication nevertheless rated their general level of pain as 'none' or 'a little'. This apparently inconsistent finding could probably be explained by a misinterpretation of the response categories employed for the item assessing the effect of pain medicine. In contrast to all other items in the QLQ-LC13, this item is positively worded, which may have been confusing to patients.

On-treatment assessment

Of 537 and 346 patients entering studies 1 and 2, respectively, 430 and 305 completed both pretreatment and on-treatment questionnaires. Thus, 17% of all patients were lost to follow-up for various reasons, including early death, disease progression and administrative failure. Withdrawal of consent (i.e. patient refusal) was an exceptional reason for not completing the second questionnaire. Pretreatment performance status was significantly worse among the subgroup of patients who were lost to follow-up as compared to patients who subsequently completed the on-treatment questionnaire ($P < 0.01$), which further points to poor health status as a major reason for patient attrition from the study (see [3, 4] for more details regarding patient loss to follow-up).

Change over time. The changes in QLQ-LC13 symptom scores from pre- to on-treatment assessment are shown in Figure 3. All mean symptom scores (merged data from studies 1 and 2) changed significantly in the expected direction, i.e. they decreased. With one exception (extra-thoracic pain in study 1), the decrease in pain scores was consistent across the two studies. Moreover, in study 2, the reported frequency of use of pain medication declined ($P < 0.05$, not in Figure 3), although the reported level of pain relief from medication remained unchanged.

For the combined patient samples, dyspnoea scores improved significantly over time, although analysis of the two studies separately indicated that this improvement was confined primarily to patients from study 1. The mean scores for coughing and haemoptysis also declined significantly over time.

As hypothesised, the scores for QLQ-LC13 items relating to treatment side-effects—including sore mouth, trouble swallowing, neuropathy symptoms and hair loss—increased significantly from pre- to on-treatment assessment (Figure 4). The magnitude of these changes was similar across the two study samples.

Change over time by performance status. The QLQ-LC13 symptom scores were also analysed with regard to responsiveness to change in health status, as approximated by performance status scores. For this purpose, the patient sample was subdivided into

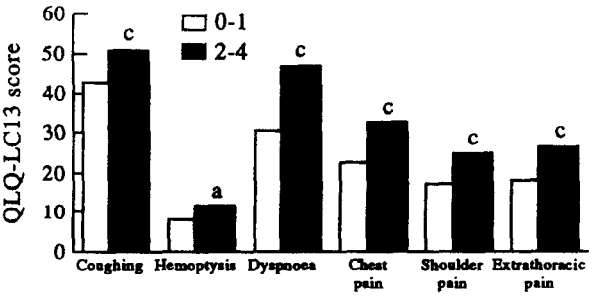

Figure 2. Pretreatment QLQ-LC13 symptom scores (merged data from studies 1 and 2) by performance status, recoded into two levels (0–1 versus 2–4). The levels of statistical significance are indicated with a ($P < 0.05$), b ($P < 0.01$), or c ($P < 0.001$); factorial analysis of variance.

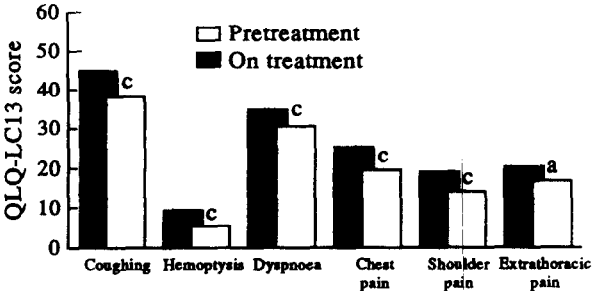

Figure 3. Pre- and on-treatment QLQ-LC13 symptom scores (merged data from studies 1 and 2). Only data referring to the patient subsamples that were measured twice ($n = 735$) are included in the analysis. The levels of statistical significance are indicated with a ($P < 0.05$); b ($P < 0.01$) or c ($P < 0.001$); repeated measures analysis of variance.

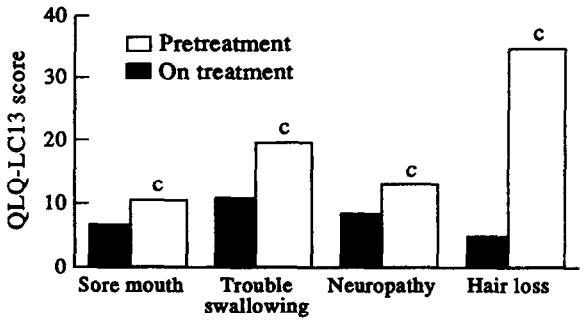

Figure 4. Pre- and on-treatment QLQ-LC13 toxicity scores (merged data from studies 1 and 2). Only data referring to the patient subsamples that were measured twice (n = 735) are included in the analysis. The levels of statistical significance are indicated with a ($P < 0.05$); b ($P < 0.01$) or c ($P < 0.001$); repeated measures analysis of variance.

three groups: those whose performance status had improved at least one level during treatment, those with unchanged performance status, and those whose performance status had deteriorated at least one level. A repeated measures analysis of variance revealed significant interaction effects (group differences over time) for dyspnoea ($P < 0.001$), chest pain ($P < 0.01$) and coughing ($P < 0.01$). For the remaining symptoms, there was a non-significant trend in the expected direction.

Change over time by treatment modality. The relationship between treatment and side-effect scores over time was evaluated similarly, employing a repeated measures ANOVA with treatment modality as the grouping factor (chemotherapy versus radiotherapy; 19 patients with combined treatment were excluded from this analysis). Significant increases in hair loss and peripheral neuropathy were noted for those patients undergoing chemotherapy, while increasing difficulties with swallowing were reported primarily by patients receiving radiotherapy ($P < 0.001$, respectively). Increasing problems with a sore mouth or tongue were not specifically associated with either of the two treatments.

The self-reported on-treatment QLQ-LC13 side-effects were also compared with the corresponding physicians' ratings on the WHO toxicity scales. Correlations ranged from 0.19 for oral toxicity to 0.73 for hair loss, all statistically significant ($P < 0.001$).

Effect on quality of life

The relative contribution of individual QLQ-LC13 items to explaining the variance in global quality of life ratings was estimated by means of a stepwise multiple regression analysis, including 12 of the QLQ-LC13 items (the item on pain medication was excluded) as independent variables. Twenty-five per cent of the variance in pretreatment global quality of life scores was explained by haemoptysis, effort dyspnoea, trouble with swallowing and pain in the chest, shoulder or other sites (multiple $R = 0.50$). Coughing, resting dyspnoea, sore mouth, peripheral neuropathy and hair loss did not enter into the multivariate model. Similar results were observed at the on-treatment evaluation, except that neuropathy was substituted for extrathoracic pain in the stepwise multiple regression model.

DISCUSSION

The EORTC modular system for assessing the quality of life of patients participating in cancer clinical trials is composed of two basic elements: (1) a core quality of life questionnaire covering basic components of health-related quality of life relevant to a wide range of patient populations; and (2) additional questionnaire modules designed to provide information on specific diagnosis- or treatment-related issues.

When employed with a culturally diverse sample of lung cancer patients, the current, second generation core questionnaire, QLQ-C30, has proven to be a practical, reliable and valid indicator of patients' quality of life, and to be responsive to changes in patients' health status over time. Moreover, the psychometric performance of the questionnaire has been shown to be consistent across cultural groups, lending support to its usefulness in multinational research settings [4].

In this paper, we have reported on the international field testing of the lung cancer-specific questionnaire module, QLQ-LC13, designed to supplement both the QLQ-C30 and its antecedent, the QLQ-C36. The findings indicate that the questionnaire items and scales pertaining to symptoms of lung cancer discriminate clearly between patient subgroups differing in initial performance status and, to a more limited extent, between subgroups formed on the basis of disease stage. Similarly, those items pertaining to treatment toxicity were found to discriminate between subgroups of patients receiving chemotherapy versus radiotherapy.

As expected, an overall pattern of change over time was observed in QLQ-LC13 scores, with patients reporting a decrease in disease symptoms and an increase in treatment side-effects. However, responsiveness of the QLQ-LC13 to change in performance status was noted only for those items assessing chest pain, dyspnoea and coughing. There are several possible explanations for the weak association observed between changes from pretreatment to on-treatment in self-reported levels of coughing, haemoptysis, shoulder pain and extrathoracic pain on the one hand, and changes in performance status on the other. First, it is known that non-surgical treatment in advanced lung cancer may result in rapid symptom relief in responding patients [10], primarily due to local disease control. Improvement of functional status occurs typically, if at all, over a longer period of time. In both field studies, follow-up measurements were carried out rather early in the treatment process. Thus, while one might expect to observe improvement in self-reported symptoms (as was the case in both studies), this would not necessarily be reflected in improved performance status. Second, while performance status ratings have been shown to be an important prognostic factor in lung cancer [11, 12], the responsiveness of such ratings to changes in patients' level of functioning over time has yet to be demonstrated. Third, the large majority of the patients in the current studies received a pretreatment performance status rating of 0 or 1, indicating that only marginal improvements in functioning could be expected over time. This suggests that the rapid improvement observed in patients' self-reported symptom levels may very well be clinically meaningful, despite the lack of corresponding changes in performance status.

An important question is whether the QLQ-LC13 provides information that would otherwise not be captured by the core quality of life questionnaire. This is clearly the case for coughing and haemoptysis, as neither symptom is included in the core questionnaire. While dyspnoea is covered by a single item in the core questionnaire, its high prevalence among lung cancer patients and, perhaps more importantly, its potential impact on patients' level of functioning and well-being, recommended the use of a multi-item scale. Combined with the general dyspnoea

item of the core questionnaire, the QLQ-LC13 items on dyspnoea formed a scale with excellent reliability and validity.

For similar reasons, it was deemed appropriate to supplement the pain item(s) in the core questionnaire with additional items addressing specific sites of pain, as well as the use and perceived effectiveness of pain medication. Although the results did not support combining the site-specific pain scores into a multi-item scale, when employed individually, these items were found to vary significantly as a function of disease stage. However, the item on perceived medication effectiveness proved to be problematic, probably due to its positive wording. This item was clearly misinterpreted by many patients, resulting in a number of inconsistent response patterns. Taken together, these findings suggest the need for further work on the assessment of pain within the QLQ-LC13.

The toxicity items of the QLQ-LC13 were selected to reflect treatment side-effects that are common among lung cancer patients receiving either conventional chemotherapy or radiotherapy. None of these items is included in the core questionnaire.

Hair loss was the most prevalent chemotherapy-related side-effect reported by patients. Interestingly though, it did not contribute significantly to explaining the variance in global quality of life ratings. In part, the apparent lack of impact of hair loss on quality of life may be due to the predominance of older males in this population of patients. It may also be that patients anticipate this side-effect, are aware of its transitory nature, and thus are less troubled by it.

Peripheral neuropathy was reported by relatively few patients in the current study. As this symptom typically emerges only over a longer period of time, it probably had not reached its maximum level at the time of the on-treatment assessment. Despite its low prevalence, peripheral neuropathy explained a significant amount of the variance in global quality of life ratings. This is all the more striking given that the QLQ-LC13 assesses only mild complaints (i.e. tingling hands or feet). In future versions of the questionnaire, it may be useful to include additional items reflecting moderate to severe grades of neuropathy. The resulting impairment in terms of loss of feeling and strength could be expected to have even greater impact on patients' level of functioning and overall quality of life ratings [13].

As expected, trouble with swallowing was associated significantly with radiotherapy. It also contributed significantly to explaining the variance in global quality of life ratings. In comparison with other toxicity scores, the pretreatment level on this symptom was relatively high, indicating that it is related to both treatment and to the underlying disease.

Finally, a sore mouth or tongue was found to be a relatively non-specific symptom. Although, as expected, this complaint was more pronounced during treatment, it was not related specifically to chemotherapy (as had been hypothesised). Additionally, self-reported irritation in the oral cavity correlated poorly with the corresponding WHO ratings of oral toxicity as provided by the physicians, suggesting the need for direct patient assessment of this complaint.

In conclusion, the results of the current analysis support the clinical validity and usefulness of the EORTC QLQ-LC13 as a supplementary measure of symptoms and side-effects experienced by lung cancer patients receiving non-surgical treatment. Although the results point to some areas in which the questionnaire could benefit from further refinement, these are of a relatively minor nature. Additional work is also needed to examine the performance of this questionnaire module over a longer period of time, in prospective, longitudinal studies. While such revisions and testing are being pursued, we recommend that the current version of the QLQ-LC13 be employed as a supplement to the core questionnaire, the QLQ-C30, in clinical trial-based quality of life investigations in lung cancer.

1. Aaronson NK, Bakker W, Stewart AL, *et al.* Multidimensional approach to the measurement of quality of life in lung cancer clinical trials. In Aaronson NK, Beckmann JH, eds. *The Quality of Life of Cancer Patients*. New York, Raven Press, 1987, 62–82.
2. Aaronson NK, Bullinger M, Ahmedzai S. A modular approach to quality of life assessment in cancer clinical trials. In *Recent Results in Cancer Research*. Berlin, Springer-Verlag, 1988, 231–249.
3. Aaronson NK, Ahmedzai S, Bullinger M, *et al.* The EORTC Core Quality of Life Questionnaire: interim results of an international field study. In Osoba D, ed. *Effect of Cancer on Quality of Life*. Boca Raton, CRC Press, 1991, 185–203.
4. Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993, **85**, 365–376.
5. Zubrod CG, Schneidermann M, Frei M, *et al.* Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylen thiophosphoramide. *J Chron Dis* 1960, **11**, 7–33.
6. WHO. *Handbook for Reporting Results of Cancer Treatment*. Geneva, WHO, 1979.
7. Likert R. A technique for the measurement of attitudes. *Arch Psychol* 1932, **140**, 1–55.
8. Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrica* 1951, **16**, 297–334.
9. Kerlinger FN. *Foundations of Behavioral Research*. New York, Holt, Rinehart and Winston, 1973.
10. Lau M. *Quality of Life in Lung Cancer Patients—With Special Reference to Small Cell Lung Cancer*. Copenhagen, FADL's Forlag, 1988.
11. Stanley K. Prognostic factors for survival in patients with inoperable lung cancer. *J Natl Cancer Inst* 1980, **65**, 25–31.
12. Ihde DC, Hansen HH. Staging procedures and prognostic factors in small cell carcinoma of the lung. In Greco F, Oldham R, Bunn P, eds. *Small Cell Lung Cancer*. New York, Grune and Stratton, 1981, 261–283.
13. Bergman B, Sullivan M, Sörenson S. Quality of life during chemotherapy for small cell lung cancer. I. An evaluation with generic health measures. *Acta Oncol* 1991, **30**, 947–957.

Acknowledgements—The authors would like to acknowledge the contribution of the following individuals to this study: M. Andersson, University of Umeå, Umeå, Sweden; J. Auchterlonie, Western General Hospital, Edinburgh, U.K.; J. Bernhard, Medical Division Lory, Bern, Switzerland; M. Bullinger, Biometric Center for Therapeutic Studies, Munich, Germany; H. Clemm, University of Munich, Munich, Germany; J.B. Cookson, Glenfield General Hospital, Leicester, U.K.; M.A. Cornbleet, Western General Hospital, Edinburgh, U.K.; D. Crabeels, EORTC Central Office and Data Center, Brussels, Belgium; A. Cull, ICRF Medical Oncology Unit, Edinburgh, U.K.; J.C.J.M. de Haes, Academic Medical Center, University Hospital, Amsterdam, the Netherlands; N. Delvaux, Institut Jules Bordet, Brussels, Belgium; A. Depierre, Centre Hospitalier Régional, Besançon, France; N.J. Duez, EORTC Central Office and Data Center, Brussels, Belgium; J. Estapè, Dept of Medical Oncology, Clinical Hospital of Barcelona, Barcolona, Spain; Ch. Farvacques, Institut Jules Bordet, Brussels, Belgium; A. Filiberti, Institutu Nationale Tumori, Milan, Italy; H. Flechtner, University of Cologne, Cologne, Germany; S.B. Fleishman, Long Island Jewish Medical Center, New Hyde Park, New York, U.S.A. (for the Cancer and Leukemia Group B); U. Frick, Biometric Center for Therapeutiv Studies, Munich, Germany; J. García-Conde, University Clinical Hospital, Valencia, Spain; K. Gebert, University of Munich, Munich, Germany; A. Gregor, Western General Hospital, Edinburgh, U.K.; M. Groenvold, University of Copenhagen, Copenhagen, Denmark; M. Heim, Mannheim Clinic Oncological Center, Mannheim, Germany; P. Hopwood, CRC Psychological Medicine Group, Manchester, U.K.; Ch. Hürny, Institute for Medical Oncology, Bern, Switzer-

land; M. Kerekjarto, University Hospital Eppendorf, Hamburg, Germany; M. Klee, Rigshospitalet, Copenhagen, Denmark; F. Kraft, Medical University Clinic, Freiburg, Germany; T. Küchler, University Hospital Eppendorf, Hamburg, Germany; B. Lebeau, Hospital Saint-Antoine, Paris, France; R.C.F. Leonard, Western General Hospital, Edinburgh, U.K.; A. Lobo, University Hospital Clinic, Zaragoza, Spain; F.J.F. Madden, Leicester Royal Infirmary, Leicester, U.K.; M. Mastilica, University of Zagreb, Zagreb, Croatia; G. Mendl, University of Munich, Munich, Germany; R.N. Murray, British Columbia Cancer Agency, Vancouver, Canada; E. Nou, Academic Hospital, Uppsala, Sweden; D. Osoba, British Columbia Cancer Agency, Vancouver, Canada; B. Pfausler, University Hospital of Innsbruck, Innsbruck, Austria; D. Razavi, Institut Jules Bordet, Brussels, Belgium; P.B. Rofe, Royal Adelaide Hospital, Adelaide, Australia; L. Salvador, Clinic Hospital of Barcelona, Barcelona, Spain; S. Schraub, Centre Hospitalier Regional de Besançon, Besançon, France; J.P. Sculier, Institut Jules Bordet, Brussels, Belgium; A. Shah, British Columbia Cancer Agency, Vancouver, Canada; J.F. Smyth, Western General Hospital, Edinburgh, U.K.; K. Sneeuw, the Netherlands Cancer Institute, Amsterdam, the Netherlands; L.A. Solé-Calvo, Hospital Vall d'Hebrón, Barcelona, Spain; A.F. Stewart, University of California, San Francisco, U.S.A.; F. Takeda, Saitama Cancer Center, Saitama, Japan; F.S.A.M. van Dam, the Netherlands Cancer Institute, Amsterdam, the Netherlands; P. van Houtte, Institut Jules Bordet, Brussels, Belgium; F. von Bültzingslöwen, Fachklinik für Erkrankungen der Atmungsorgane, Donaustauf, Germany; N. Vranes, Clinical Hospital for Lung Disease, Zagreb, Croatia; D. Warr, Princess Margaret Hospital, Toronto, Canada; K. Yoshida, Saitama Cancer Center, Saitama, Japan; R. Zittoun, Hotel-Dieu de Paris, Paris, France.

Pergamon

European Journal of Cancer Vol. 30A, No. 5, pp. 642–645, 1994
Elsevier Science Ltd
Printed in Great Britain
0959–8049/94 $7.00 + 0.00

0959-8049(93)E0082-F

Is There Potential for Granulocyte or Granulocyte–Macrophage Colony Stimulating Factors in Radiotherapy?

P. Janssens, C. Mitine, M. Beauduin and P. Scalliet

The purpose of this communication was to explore which situations in radiotherapy might benefit from concomitant administration of haematopoietic growth factors (HGF). Only large-field radiotherapy is likely to induce bone marrow depression, such as irradiation of Hodgkin's disease. Therefore, we studied 122 patients irradiated for Hodgkin's disease, looking at peripheral blood cell count before, during and after the treatment. One hundred and four treatments were preceded by chemotherapy (MOPP and/or ABVD) and the radiation dose was between 36 and 44 Gy in 2 Gy per fraction sessions. Severe leucopenia (grade III WHO) was very uncommon and justified treatment interruption only twice. In both cases, it was paired with thrombocytopenia. No infection developed. It is concluded that when radiotherapy is used alone, prophylactic use of HGFs does not seem justified. This, of course, does not apply to radiochemotherapy combinations, although thorough investigations in this field are still awaited.

Key words: growth factors, Hodgkin's disease, radiotherapy
Eur J Cancer, Vol. 30A, No. 5, pp. 642–645, 1994

INTRODUCTION

GRANULOCYTE AND granulocyte–macrophage colony stimulating factors (G-CSF and GM-CSF, further referred in the text as haematopoietic growth factors, HGFs) have recently become commercially available. Their ability to improve tolerance to cytotoxic chemotherapy, so that preplanned drug dosages can be delivered without excessive haematological toxicity, has been perceived as a major improvement in haematology and oncology. Moreover, antibiotics and/or hospitalisation needs, resulting from neutropenia-related infections, seem to be reduced, a fact of great importance in European countries where hospitalisation is very expensive [1].

HGFs, however, are very expensive products themselves. A typical filgrastim (Neupogen®) treatment costs between 1500 and 2000 ECU in Belgium. There has thus been great concern about the potential impact of an unlimited use of HGFs on public health budgets, since cancer is a widespread disease and chemotherapy a widespread treatment of cancer. In particular, health care administrations fear that the global impact on health budgets of an unrestricted use of HGF might far outweigh the savings which its use is supposed to bring. Belgian authorities

Correspondence to P. Scalliet.
P. Janssens and P. Scalliet are at the Department of Radiation Oncology, Antwerp University (UIA), AZ Middlelheim, Lindendreef, I, B-2020 Antwerp, Belgium; C. Mitine and M. Beauduin are at the Centre of Oncology, Hopital de Jolimont, Haine St Paul, Belgium.
Revised 15 Dec. 1993; accepted 21 Dec. 1993.