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Eur J Cancer, Vol. 26, No. 4, pp. 484–492, 1990.
Printed in Great Britain
0277–5379/90$3.00 + 0.00

Quality of Life During Chemotherapy for Small Cell Lung Cancer: Assessment and Use of a Daily Diary Card in a Randomized Trial

Duncan M. Geddes, Leanne Dones, Elizabeth Hill, Kate Law, Peter G. Harper, Stephen G. Spiro, Jeffrey S. Tobias and Robert L. Souhami

Fifty-three patients who were taking part in a randomized trial of chemotherapy in small cell lung cancer (SCLC) were entered into a study of quality of life measurement using a daily diary card. Patients received either four or eight cycles of initial chemotherapy and daily records were scored, using a four point scale of nausea, sickness, appetite, sleep, mood, pain, activity and general well being. Two hundred and fifty-six of a possible 379 cards were returned (68% compliance). The first 31 patients took part in an assessment of the diary card where comparison was made with nurse ratings using the card, the EORTC questionnaire and the Spitzer quality of life index. These comparisons showed appropriate convergent and divergent validity and demonstrated the sensitivity of the diary card to short term changes compared with the other measures.

In the randomized trial the diary card demonstrated a worsening of sickness and related variables as treatment continued. This spilled over into mood and general well being although physical variables of pain, sleep and activity were largely unaffected. Prophylactic cranial irradiation was associated with a transient increase in sickness and vomiting.

The study shows that the diary card is an instrument sensitive to short term changes in quality of life and thus especially useful for comparing effects during the period of treatment.
Eur J Cancer, Vol. 26, No. 4, pp. 484—492, 1990.

INTRODUCTION

THERE IS increasing recognition that the measurement of quality of life is an essential part of trials in the treatment of cancer. This is especially important when survival is likely to be short and the treatment administered has appreciable toxicity. The problems involved in measuring quality of life in cancer have been well reviewed by Fayers and Jones [1] and while a number of instruments have been proposed, none has yet become generally accepted as the best. Comprehensive health status questionnaires such as the sickness impact profile [2] and Index of Wellbeing [3] scales have been well validated and tested in a range of different diseases but these instruments are complex to administer, require dedicated staff and are not well suited to repeated use over a short period. In contrast the simplest measures of all such as the Karnovsky [4] and ECOG scores are very easy to administer but are seriously limited in scope. Between these two extremes a number of other instruments have been tried such as the EORTC questionnaire [5] and the Spitzer quality of life index [6].

None of these instruments is ideally suited to the chemotherapy of small cell lung cancer (SCLC) as in this condition median survival is usually less than 1 year, in spite of a good chemotherapy response, and drug toxicity can be considerable. The EORTC questionnaire contains 47 questions and cannot be administered frequently. The Spitzer index assesses five variables only. In evaluating two different treatments consideration has to be given to the symptoms of the disease, the side effects of treatment and the effect of both on the patient's

Correspondence and reprint requests to R.L. Souhami.
Duncan M. Geddes, Elizabeth Hill and Stephen G. Spiro are at Brompton Hospital, Fulham Road, London SW3 6HB, Leanne Dones is at the Clinical Operation Research Unit, University College London, Gower Street, London WC1E 6AU, Kate Law, Jeffrey S. Tobias and Robert L. Souhami are at the Department of Radiotherapy and Oncology, University College Hospital, Gower Street, London WC1E 6AU, and Peter G. Harper is at the Department of Oncology, Guy's Hospital, St. Thomas' Street, London SE1 9JR, U.K.

mood, general well being and activity. Furthermore, frequent measurements need to be made, as both the symptoms of the disease and the side effects of treatment change often and rapidly. We have therefore used a daily diary card modelled on that designed by the MRC [7]. This card provides daily assessments of aspects of quality of life and, by so doing, gives information more responsive to short term changes than other measures. We have assessed its use by comparing the patient's scores with those of a research nurse. We have attempted to compare the results obtained with the card with the EORTC questionnaire and the Spitzer index although, because the methods provide different kinds of information, the value of such comparisons is limited.

We also report here the results of the use of the card in determining aspects of quality of life during a randomized trial of chemotherapy duration in SCLC [8]. The trial was designed to assess the optimum length of chemotherapy in the disease. Four cycles of initial chemotherapy were compared with eight. This design allowed a direct comparison of quality of life between those patients who were receiving cycles 5–8 and matched patients who completed their treatment after four cycles. The results of this trial have been reported separately [8]. The quality of life data reported here demonstrate the possibilities and difficulties in this kind of measurement in a randomized trial of two chemotherapy programmes.

PATIENTS AND METHODS

Patients

Fifty-three consecutive patients who were taking part in a randomized trial of chemotherapy were entered into the quality of life study. This multi-institution trial took place between February 1982 and September 1985. The quality of life study was conducted on a cohort of patients from three of the participating institutions between March 1984 and February 1985. The first 31 patients also took part in the comparison of the diary cards with other measures. Following diagnosis and staging the patients were stratified according to disease extent and then randomized to receive either eight or four courses of chemotherapy given at 3-weekly intervals (Groups 1 and 2 respectively) (Fig. 1). Chemotherapy was cyclophosphamide 1 g/m^2, vincristine 1.4 mg/m^2 both given intravenously on day 1 and etoposide 100 mg, 8 hourly by mouth on days 1, 2, 3. This treatment was continued while the patient had stable or responding disease. On relapse or progression the patients were allocated to receive either second line chemotherapy or symptomatic treatment only.

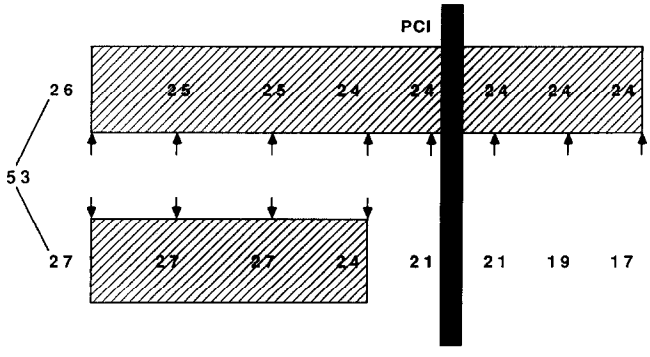


Fig. 1. Study design. Arrows indicate chemotherapy cycles. Numbers indicate the number of patients who were progression free at each point and continued in the quality of life study.

Prophylactic cranial irradiation (PCI) (20 Gy in five fractions over 5–7 days) was given to all patients who were assessed as having a partial or complete response 3 weeks after the fourth course of chemotherapy.

Methods

1. *Description of diary card.* At the time of diagnosis, a research nurse gave each patient a diary card and showed them how to complete it daily at the end of each day. Each card covered a period of 4 weeks and was collected at a hospital visit when a new card was supplied. The card was a modification of that designed by the U.K. Medical Research Council for use in cancer treatment trials. Eight questions were asked and the patients responded by choosing the most appropriate answer on a four point categorized scale and indications of the states corresponding to each score were provided on the card (Fig. 2). These questions were chosen as being likely to detect aspects of quality of life associated with treatment-based toxicity, and as a result of past experience with the MRC diary card.

The questions were designed to cover three categories: symptoms related mainly to treatment—sickness, vomiting, appetite; symptoms related to disease—pain; general assessment—mood, sleep, activity, general well being. Days 1–3 are the *treatment period*. Days 4–21 of the cycle are referred to as the *inter-treatment period*.

2. *Methods of assessment.* For the first 31 patients we carried out a detailed assessment of the diary card compared with other widely used measures. Quality of life was measured using the Spitzer quality of life index [6] and the EORTC quality of life questionnaire [5]. These were completed by the nurse every 3 weeks when the patients attended hospital and on one occasion at home when the patients was visited by a research nurse halfway between two courses of chemotherapy. At each hospital visit the research nurse recorded a Karnovsky Performance Status (PS) score for each patient. At the time of the home visit the research nurse also completed the diary card, independently of the patient, basing her scores on an informal interview. Cohen's kappa statistic was used to test the level of agreement between the patients' and the interviewer's score on the diary card.

PLEASE ANSWER THE FOLLOWING QUESTIONS.
WRITE DOWN THE NUMBER OF YOUR ANSWER
IN THE APPROPRIATE BOX OPPOSITE THIS PAGE

WEEK 1

	Mon	Tues	Wed	Thur	Fri	Sat	Sun
DID YOU FEEL SICK TODAY? 1. Not at all 2. Occasionally 3. A lot 4. All the time							
DID YOU VOMIT TODAY? 1. Not at all 2. Once 3. Twice 4. More than twice							
HOW GOOD HAS YOUR APPETITE BEEN TODAY? 1. Good 2. Fair 3. Poor 4. Bad							
HOW MUCH PAIN HAVE YOU HAD TODAY? 1. None 2. A little 3. Quite a lot 4. A lot							
HOW DID YOU SLEEP LAST NIGHT? 1. Very well 2. Quite well 3. Badly 4. Not at all							
HOW HAPPY HAVE YOU BEEN TODAY? 1. Happy 2. Fairly happy 3. Unhappy 4. Very unhappy							
HOW ARE YOU FEELING GENERALLY? 1. Well 2. Fair 3. Poor 4. Very poor							
WHAT DID YOU DO TODAY? 1. Stayed in bed 2. Got up – did nothing 3. Light work/House work 4. Fully active							

Fig. 2. The daily diary card.

Table 1. Aggregation of EORTC questions for comparison with the diary card

Dairy card category	EORTC questions							
Sickness	9							
Vomiting	13	18						
Appetite	1							
Pain	5	12	19	27	28	33	36	
Sleep	11							
Mood	2	4	6	8	10	16	17	20
General well being	3	14	15	21–26		29–32	34	35
Activity	7	38–41						

Questions 42–45 inclusive refer to specific therapies and questions 37, 46 and 47 were not suitable for comparisons with the diary card.

The diary card was compared with the EORTC questionnaire using the criteria of Campbell and Fisk [9] to test for convergent and discriminant validity. Essentially, the method involves comparing correlations between measurements made by two different instruments to see whether those purporting to measure the same thing, do so (convergent validity), and those which do not are different (discriminant validity). In order to do this it was necessary to combine the 47 questions in the EORTC questionnaire into sections or components that could be regarded as similar to the categories of the diary card. The way in which this was done is detailed in Table 1.

The quality of life index (Spitzer) was compared with the diary card. It was not possible to apply Campbell and Fisk criteria strictly to these forms as they were not measuring quality of life by the same criteria. A simple assessment of the correlation matrix was therefore used.

3. *Use of diary card in the randomized trial.* Fifty-three consecutively randomized patients were assessed from the start of chemotherapy using the diary card. Patients with very poor performance status (< 70%) were excluded since it was felt that the diary card might prove too difficult to complete. The methods described above were used except that a few patients who received some of their chemotherapy at another hospital were, after initial instruction, given 3 months supply of cards and returned them by post at 3 weekly intervals.

The aim of the trial was to determine if there was a difference in survival when initial chemotherapy of two different durations was used. The purpose of the quality of life assessment was only to assess if there was a difference in quality of life in patients

Table 2. Median survival in entire trial according to randomization

Treatment group	Median survival (weeks)	2-year survival
Long initial CT	39	3.7
(a) Relapse CT	42	3.5
(b) Symptomatic	38	4.0
Short initial CT	32	4.0
(a) Relapse CT	38	5.6
(b) Symptomatic	30*	2.8

*Short and symptomatic significantly worse median survival ($P > 0.05$) than all other randomizations.

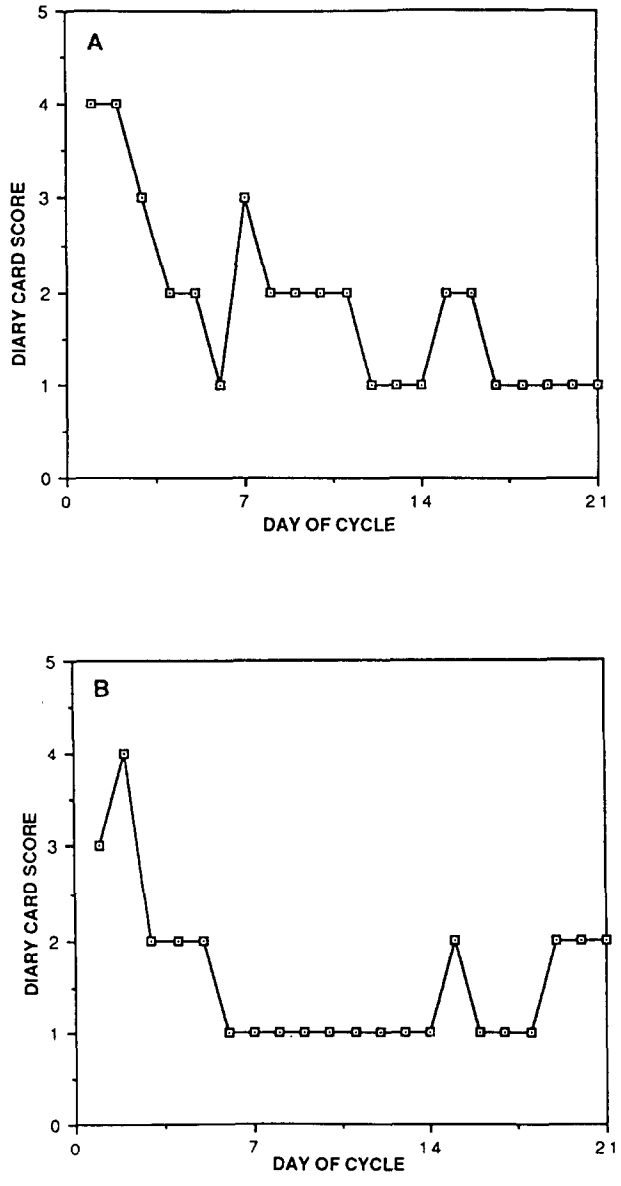


Fig. 3. Single patient's record of the three weeks following a course of chemotherapy. A: Scores for appetite. B: Scores for mood.

Table 3. Patient characteristics in the whole trial and in the quality of life study

	Trial		Study group	
	Long	Short	Long (Group 1)	Short (Group 2)
No	305	305	26	27
Age–Median	63	63	62	63
Range	34–74	31–74	47–72	34–73
Limited/extensive (%)	33/67	31/69	31/69	30/70
M/F (%)	61/39	67/33	73/27	70/30
Performance status 80–100%	77%	71%	95%	92%
< 80%	23%	29%	5%	8%
% Response (CR + PR)	61%	61%	81%	85%

who *did not have disease progression* but who either stopped chemotherapy after four cycles or continued for eight. The intention was to try to balance the advantages and disadvantages of continuing chemotherapy against any survival difference. Patients were therefore assessed, whether chemotherapy was continued or stopped, until there was disease progression. The two arms of the study do not differ until after four cycles and the clinical comparison is only of interest after that point. The data derived independently in the two arms of the study during the first four cycles give a useful check of reproducibility of the method.

In making the comparison between the two treatment arms, the diary cards were analysed by examining the proportions of patients whose replies fell into the categories > 1, > 2 and > 3. Differences in proportions were regarded as significant if $P < 0.05$. To test the hypothesis that reactions to therapy were changing from cycle to cycle the proportion of patients scoring > 2 on the day after chemotherapy were plotted against the cycle number and a regression line fitted to test whether the slope was non-zero. Mean scores are not used since these do not give a measure of the proportion of patients having a significant symptom. Non-parametric (Mann–Whitney) statistical methods were used in comparing results.

RESULTS

The full results of this trial including survival data have been published separately [8]. The differences in median survival in the trial are given in Table 2 and the characteristics of the patients studied in this report and in the whole trial are shown in Table 3. The study patients are representative of the trial as a whole except in respect of performance status (PS) with a greater proportion of patients PS 0–1 in the study group. This is reflected in a higher response rate in the study group compared with the trial as a whole. However the two arms of the study group (long vs. short chemotherapy) are evenly matched.

1. *Analysis of diary card results*

Compliance during the validation period of study was good, 85% of all possible diary card questions were completed and available for analysis. When the data from the entire study are included the compliance rate was 68%. Figure 3 shows graphically the scores for appetite and mood of a single patient during a single treatment cycle. The sensitivity of the method to daily changes is apparent with an expected marked deterioration in these measures during the treatment period (days 1–3)

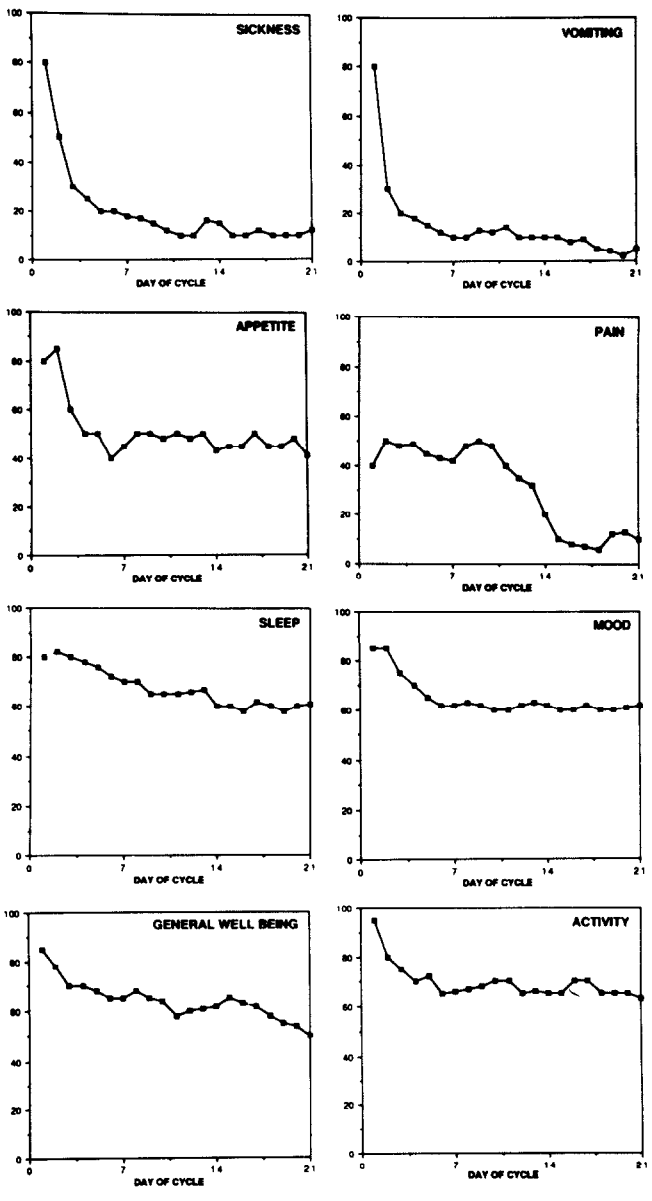
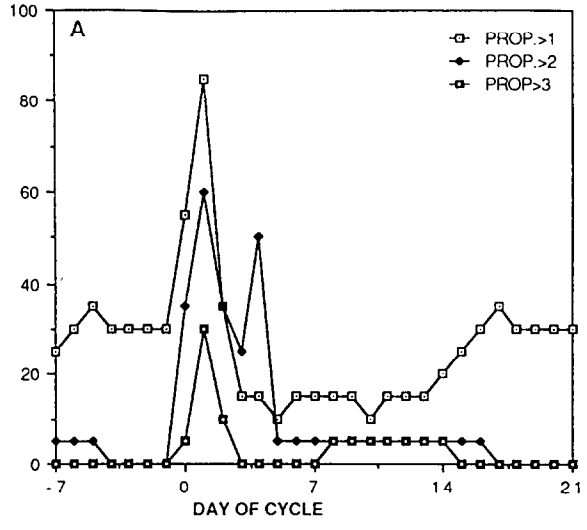


Fig. 4. Proportion (%) of diary card replies in category 2 or more according to the day in the treatment cycle. Chemotherapy was given on days 1–3. All treated patients and all courses combined.

but some persistence of symptoms in the inter-treatment period (days 4–21). These short term changes would not be detectable by the other methods.

Figure 4 shows each variable, according to day in treatment cycle, for all patients combined. This analysis is made by showing the proportion of patients who gave a response of 2 or more to each of the questions. The pattern was similar for all diary card questions except pain. There was a sharp deterioration at the time of chemotherapy but no worsening in the few days before. The second day of chemotherapy was the worst (the drugs were usually given in the afternoon or evening of day 1) and improvement towards the base line levels occurred on day 4 when no chemotherapy was given. The worsening of mood, sleep, activity and general well being demonstrate clearly how the specific side effects of chemotherapy (vomiting and sickness) extend to affect other aspects of the patient's quality of life (mood, activity, general well being) which are not immediately related to drug toxicity. Analysis of the proportion scoring 1 or more shows the same general trend for most symptoms (such as vomiting—Fig. 5A), but for some, such as sleep, there is a high proportion of patients reporting minor changes throughout the cycle, but more severe disturbance is confined to the treatment days (Fig. 5B). It should be noted that scoring for activity is opposite in direction to that of the other variables (a high score is better activity).



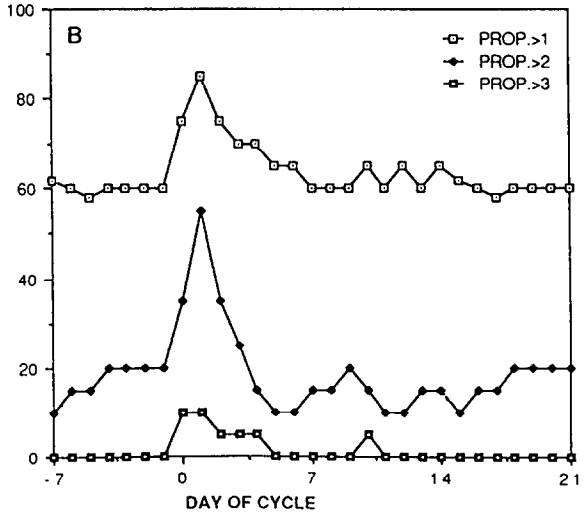


Fig. 5. Proportion (%) of diary card replies in categories of > 1, > 2, > 3, 7 days before treatment to 21 days following treatment. All treated patients and all courses combined. A: Scores for vomiting. B: Scores for sleep.

2. *Results of validation*

A. *Interviewer vs. patient assessment.* Cohen's kappa was computed for each of the diary card variables (Table 4). All variables were significantly different from zero ($P < 0.01$). This, however, is the very least that would be hoped for (a more than chance agreement between the two scores). Vomiting could not be properly assessed as patients did not report vomiting at the time of a home visit halfway between treatments. Table 4 also shows the percentage of cases in which there was complete agreement between the patients and the interviewer's assessment for each category. On average there was complete agreement in 71% of assessments made.

B. *Comparison of EORTC and daily diary card* (Table 5). Using the Campbell and Fisk method, four of the eight variables displayed convergent validity (pain, sleep, mood and activity) and two showed divergent validity—activity and sleep. Vomiting was not recorded at the time of admission when the assessment was made and so is not included in the analysis. General well being is not specifically assessed in the EORTC questionnaire and the aggregation of a number of different questions to compare with this diary card question is of doubtful value. The lack of strong correlation for sickness was probably due to the EORTC assessment being made at time of admission, before chemotherapy was given, while the diary card was scored in the evening.

C. *Diary card vs. Spitzer* (Table 6). The most highly correlated variables were Spitzer activity and diary card activity while the Spitzer activity score also correlated with appetite and pain. Conversely the diary card activity also correlated with Spitzer daily living and health. Sleep, mood and general well being did not correlate highly with any Spitzer variables and Spitzer outlook did not correlate with any daily diary variables. Diary card appetite correlated surprisingly widely.

Table 4. Level of agreement between patients and independent interviewer (kappa) and percentage occurrence of complete agreement between patient and nurse

Variable	Kappa	% complete agreement
Sickness	0.88	86
Appetite	0.58	67
Pain	0.76	71
Sleep	0.62	65
Mood	0.69	76
General well being	0.60	69
Activity	0.65	61

Table 5. Correlation matrix for diary card and EORTC questionnaire (aggregated as shown in Table 1). Vomiting is omitted as it did not occur at the time of the comparison. Figures in bold indicate convergent validity

	EORTC					
	Sickness	Appetite	Pain	Sleep	Mood	Activity
Diary card						
Sickness	0.20	**0.54**	0.12	−0.2	0.00	0.31
Appetite	0.37	0.26	0.28	−0.10	0.35	0.42
Pain	0.27	0.11	**0.50**	0.07	0.27	0.18
Sleep	−0.29	−0.19	−0.14	**0.55**	−0.19	−0.04
Mood	0.09	0.06	0.22	−0.11	**0.59**	0.33
Activity	0.25	**0.52**	0.40	−0.18	0.07	**0.72**

3. *Comparison of treatment effects in the randomized trial*

Fifty-three patients entered the study and 48 of these completed the initial four courses of treatment. The patients randomized to the four courses (Group 1) and eight courses (Group 2) were well matched for age, disease extent, and response to chemotherapy (Table 3).

Forty-five patients entered the second treatment period (Group 1—courses 5–8, Group 2—no treatment). Due to disease progression, withdrawal from the study was greater in Group 2 (no treatment) so that at the end of the second treatment period diary cards had been returned by 24 patients in Group 1 compared with 17 in Group 2. Thirteen patients received PCI and nine returned diary cards at this time.

To compare the results in the two treatment arms the daily measurements in all patients were combined and analysed in two ways. The proportion of patients receiving chemotherapy whose reply was in category 2 or worse at any time during the cycle is shown in Fig. 6 according to cycle number. During cycles 1–4, when chemotherapy was the same in both groups, the diary card scores were not significantly different ($P > 0.05$) in the two arms, indicating that the method gives reproducible results. During the second period (courses 5–8) the short term side effects (days 1–4) were experienced only by Group 1 since Group 2 received no chemotherapy. Figure 6 shows that in Group 1, where chemotherapy was continued, there was a progressive increase in the proportion of patients giving replies in category 2 or more. Regression lines fitted to data in Fig. 6 for Group 1 had significant positive slopes for all measures except pain and activity indicating that each successive cycle had a worse impact on the patients' quality of life. In contrast in those not treated there was a substantial diminution in the proportion scoring 2 or more particularly with respect to sickness and vomiting but also with sleep, mood, general well being and activity.

In addition to these differences, which largely reflect symptoms in the immediate post-chemotherapy period, the baseline level of adverse replies appeared different between the groups. In the second analysis, the inter-treatment period (days 4–21) was examined by combining all replies for days 4–21 for each question and comparing groups. Significantly ($P < 0.05$) more replies were in the worse categories on Group 1 than in Group 2 for the five variables sickness, vomiting, appetite, mood and general well being during the inter-treatment period (Table 7). In contrast to the results obtained with the diary card, there were no differences in performance scores (Karnovsky) between groups 1 and 2 in either treatment period. The mean scores for Group 1 and 2 were 74.7 and 77.3 during the first treatment period and 74.2 and 78.8 during the second treatment period.

Table 6. Correlation matrix for diary card and Spitzer quality of life index. Vomiting is omitted as it did not occur at the time of comparison

	Spitzer				
	Activity	Daily living	Health	Outlook	Support
Diary card					
Sickness	−0.09	−0.03	0.03	0.23	−0.42
Appetite	**−0.51**	**−0.56**	**−0.43**	−0.04	**−0.53**
Pain	**−0.51**	−0.04	−0.15	0.22	−0.30
Sleep	−0.45	0.02	−0.11	0.03	−0.28
Mood	−0.29	−0.25	−0.14	−0.17	−0.30
General well being	−0.34	−0.24	−0.32	0.14	−0.22
Activity	**−0.68**	**−0.48**	**−0.59**	−0.08	−0.16

Note: level of activity was scored in opposite direction on the diary card and the Spitzer scale. A strong negative result (bold) therefore indicates a good correlation.

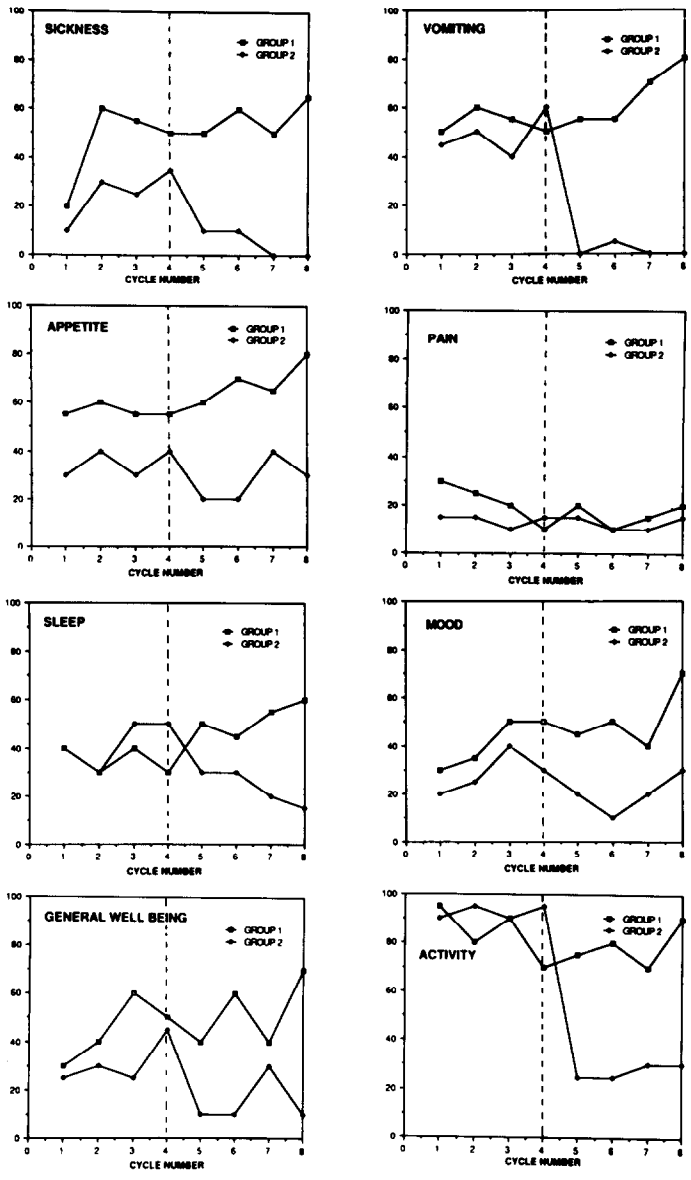


Fig. 6. Proportion (%) of diary card replies in category 2 or more following chemotherapy, according to chemotherapy course number. During courses 5–8 only Group 1 received chemotherapy. Regression line values: sickness $r = 0.8$*, sleep $r = 0.8$*, vomiting $r = 0.7$*, mood $r = 0.9$, appetite $r = 0.6$*, general well being $r = 0.9$**, pain $r = 0.02$, activity $r = 0.3$. (*$P < 0.005$; **$P < 0.001$).**

4. *Prophylactic cranial irradiation (PCI)*

The effect of PCI is shown in Table 8 in which the 7 day period of PCI is compared with an equivalent period for the same patients taken 3 weeks after PCI. In the case of patients continuing on chemotherapy the comparison was made during an inter-treatment period. There was a significant increase in sickness and vomiting during PCI with slight worsening of appetite, mood and general well being. Pain, sleep and activity were unaffected.

DISCUSSION

This is the first reported comparison of the diary card method of assessment of quality of life measures, with other techniques of assessment which are used at infrequent intervals. The results of the study showed that (a) the diary card was easy to use and compliance was satisfactory; (b) the patients' assessments and those of the research nurse were in reasonable agreement; (c) agreement between the card and two other instruments was satisfactory in some respects but comparisons were difficult. This was expected since the diary card makes more frequent measures and is therefore more sensitive to day to day changes in symptoms.

Table 7. The proportion of replies > 1 for the inter-treatment period (days 4–21). Treatment periods 5–8 combined ($P < 0.05$)*

	Group 1 (Treated)	Group 2 (Untreated)
Sickness	0.35	0.15*
Vomiting	0.15	0.05*
Appetite	0.70	0.50*
Pain	0.40	0.40
Sleep	0.60	0.50
Mood	0.80	0.60*
General well being	0.80	0.60*
Activity	0.65	0.65

Table 8. The proportion of replies > 1 over the PCI week compared with an equivalent inter-treatment week for the same patients

	PCI	No PCI	
Sickness	0.60	0.08	$P < 0.01$
Vomiting	0.21	0.06	$P < 0.02$

Maguire and Selby [10] have recently reviewed the methods which have been used to measure quality of life in cancer trials. They point out that an essential requirement of any instrument which is to be used frequently is that it is simple and sensitive to changes over time. This is especially true for an illness such as SCLC where the prognosis is poor and only short term benefits are expected from chemotherapy. All patients understood the card easily and completed it without difficulty. An overall compliance rate of 68% is reasonably good and higher than other reported studies [7]. This was, however, only achieved with a full time research nurse who gave out and collected the cards and encouraged the patients to continue filling them in. Compliance is currently running at over 90% with the employment of a new research nurse. Clearly compliance will depend to a large measure on the staff available.

The overall comparison between the patients' assessments and those of the nurse showed agreement in 71% of instances. This must be considered satisfactory especially as some of the questions refer to highly subjective variables such as appetite and mood. The only question which could not be assessed was vomiting because this was uniformly scored as 'none' at the time of the nurse interviews which took place during the inter-treatment period interview. This is not important as it is perhaps the most easy to quantify and is also represented in the sickness question.

The value of any instrument in assessing the quality of life depends closely upon the motives and intentions of the investigators. For this reason an ideal instrument is an unrealizable aim. While complex questionnaires undoubtedly probe more deeply than this diary card into different aspects of a

person's life, much of the additional information is of doubtful relevance to the patient with metastatic cancer when symptoms of the disease and the toxicity of treatment may dominate. The diary card is shown to give reproducible data which reflect the day to day variation in symptoms during chemotherapy in a way which the EORTC questionnaire cannot. For those cancer treatments where short term changes due to chemotherapy do not occur, the diary card may lose this advantage.

The sickness and vomiting reported during chemotherapy was obviously expected and demonstrate that the cards were working satisfactorily. The findings that these adverse effects spilled over to affect mood, sleep, general well being and activity was less predictable. The fact that reported pain was unchanged suggests that the questions were being answered selectively and that the deterioration of the general measures was real. More surprising was the continuation of sickness, albeit mild, throughout the inter-treatment period (days 4–21) and the parallel impairment of mood and general well being.

The comparison between the card and the EORTC and Spitzer quality of life assessments is the most difficult part of this study. Since the form and scope of the three instruments are so different, complete agreement could not be expected. Nevertheless it was encouraging that pain, sleep, mood and activity all showed good convergent validity between the diary card and the EORTC questionnaire. The EORTC aggregation for the 'general well being' comparison contained such a wide range of symptoms as to render it almost meaningless. The two variables appetite and sleep showed divergent validity which is evidence they are picking up different information and this is in line with expectations. The Spitzer correlation matrix is somewhat more difficult to analyse as only some categories assess the same variables as the diary card. Activity and appetite questions on the diary card correlated widely and may therefore be serving as 'general health status' assessments while the more specific diary card questions showed no correlation. With the exception of mood, which might have been expected to correlate with outlook, this lack of agreement is to be expected since there is little in common between the categories and indicates that the instruments are measuring different aspects of quality of life. It might therefore be reasonable to conclude that the diary card succeeds in measuring the more specific variables in the EORTC questionnaire but does not address some of the areas of information contained in the Spitzer index. This would suggest the diary card might be usefully supplemented by another more comprehensive assessment.

When used in the randomized trial, the card showed a worsening of chemotherapy side effects and less directly related variables with successive courses of chemotherapy, and a transient increase in sickness and vomiting during PCI. In evaluating these findings a number of methodological difficulties must be considered. In the first place only tentative conclusions can be drawn from measurements made on such a small number of patients. Although 53 entered the study only 45 were still completing cards at the time of course 5 and only 41 by the end of the study. Nevertheless, 256 diary cards were analysed each containing at least 160 scores. The fact that rather more patients withdrew from the study or failed to return diary cards in Group 2 compared with Group 1 illustrates a general problem of quality of life studies in cancer trials when a difference emerges between therapies. We deliberately stopped assessment on disease progression since the aim was to assess the toxicity of continued treatment and try to balance this against any survival advantage. Patients find it difficult to continue to fill in the card when they become ill with progressive disease and this poses a methodological problem for investigators who wish to assess effects throughout an entire treatment programme. This again points to the necessity to use quality of life measures which are designed to be efficient for detecting likely differences when used in comparisons between particular types of treatment. The second treatment period, during which the randomized controlled comparison was made, covered courses 5–8. The most dramatic tumour response is usually seen during courses 1–4 and so this is the time when quality of life may be most improved by treatment. The benefit of chemotherapy on symptoms has usually occurred by courses 5–8 and at this stage the adverse aspects of quality of life can be expected to be due to chemotherapy rather than to the disease.

Chemotherapy was shown to continue to diminish quality of life all through the second 3 months of treatment as compared with the controls, although the physical variables pain, sleep and activity were largely unaffected. Most previous reports have considered side effects of chemotherapy only at the time that it was given and not between cycles although Palmer and Walsh [11] gave anecdotal evidence that side effects continued. Sickness, vomiting and appetite all worsened and mood, sleep and general well being moved in parallel with no suggestion of a plateau being reached. Only the physical variables, pain and activity, were relatively unaffected. The worsening with successive courses was only apparent at the time of treatment and did not extend throughout the inter-treatment period. This finding is in conflict with the report of Priestman and Baum [12] who noted less severe symptoms at cycle 2 than cycle 1 and concluded that patients adjust to side effects with time.

There was an unequivocal increase in the frequency of reports of sickness and vomiting at the time of PCI with some possible effect on mood and general well being. Although nausea is sometimes mentioned as a non-specific effect of radiotherapy its occurrence with PCI has not been noted previously [13] and, while it may not be directly caused by PCI and could be a response to further hospital attendances, the effect on the patient remains adverse. The symptoms at this time were on the whole mild and short lived but must clearly be considered in any discussion of the role of PCI in this disease. Perhaps the most important finding is that it has not been noted before, underlying the insensitivity of most conventional measures of symptoms and quality of life. This is well demonstrated by the Karnovsky scores which did not alter over the study period and showed no differences between the groups.

This study demonstrates the acute and extended toxicity of chemotherapy and provides arguments for limiting the number of courses given, provided this does not materially affect survival. While these conclusions cannot be extended to other malignancies when chemotherapy is given for cure, they may be applicable to situations when drug treatment is given for palliation and only short survival gain. However, it must be emphasized that the comparison has been made only up to the point of relapse. The trial showed worse median survival and earlier disease progression for patients who stopped chemotherapy early [7]. In these patients a deterioration in quality of life is likely to have occurred earlier as a result of disease. The quality of life study reported here emphasises a central dilemma; namely how a deterioration in symptoms due to chemotherapy can be balanced against a modest advantage in survival and progression free interval with more prolonged treatment.

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Acknowledgements—This work has been supported by a grant from the Cancer Research Campaign. We are most grateful to Dr Peter Fayers and Mr Richard Stephens for helpful advice.

Eur J Cancer, Vol. 26, No. 4, pp. 492–495, 1990.
Printed in Great Britain

0277–5379/90$3.00 + 0.00

CSF Drug Levels for Children with Acute Lymphoblastic Leukemia Treated by 5 g/m^2 Methotrexate

A Study from the EORTC Childrens' Leukemia Cooperative Group

G. Milano, A. Thyss, F. Serre Debeauvais, G. Laureys, Y. Benoit, A. Deville, C. Dutour, A. Robert, J. Otten, C. Behar and D. Frappaz

A multicenter EORTC study was conducted in children with acute lymphocytic leukemia to determine whether 5 g/m^2 of methotrexate (MTX) (24 h i.v. infusion, four cycles) is an appropriate dosage for obtaining CSF drug concentrations approaching the critical cytotoxic level of 10^{-6} M. A total of 193 cycles were analyzed for 58 patients. At the end of the 24 h infusion, the mean MTX serum level was 65.27 ± 33.11 μM; the mean CSF MTX level was 1.47 ± 1.1 μM; no significant difference in CSF MTX levels was observed between patients with (n = 20) and those without i.v. Ara-C (n = 38). The mean CSF MTX/serum MTX ratio was 0.029 ± 0.027. CSF drug concentrations greater than or equal to 10^{-6} M were achieved in 81% of the courses. The highest level was 8.4 × 10^{-6} M. Only 5% of patients failed to achieve this drug concentration in at least one cycle. No significant correlation was observed between blood and CSF MTX levels. Mean CSF MTX levels were comparable from one cycle to another.
Eur J Cancer, Vol. 26, No. 4, pp. 492—495, 1990.

INTRODUCTION

METHOTREXATE (MTX) is of value in the treatment of children with acute lymphocytic leukemia (ALL) [1], however accurate determination of the optimal dose and schedule is still unclear [2]. This need is highlighted by requirements for control of CNS relapse, which remains an important problem in lymphoproliferative diseases [3]. For patients treated in the late seventies with less intensive induction therapy than presently used, a study on more than 500 children suggested thus intravenous intermediate-dose MTX (500 mg/m^2) given over 24 h provided less protection against CNS relapses than cranial irradiation [4]. In a more limited study, more intensive therapy (1500 mg/m^2) also failed to reduce the incidence of CNS relapse in increased risk patients [5]. These observations may have a pharmacological explanation as the ratio of drug levels between CSF and serum is close to 5% [6]. Consequently, co-administration of intrathecal (IT) MTX has commonly been used as a means of obtaining more consistent CSF MTX concentrations [7, 8]. Although the CSF drug levels obtained by IT MTX reached the potentially cytotoxic level of 10^{-6} M [9], this administration route does not result in uniform drug distribution throughout the entire CSF [10]. By contrast, systemic MTX administration results in homogeneous distri-