1. Ganzina F. 4'-Epidoxorubicin, a new analogue of doxorubicin: a preliminary overview of preclinical and clinical data. *Cancer Treat Rev* 1987, **10**, 1–22.
2. Kalman LA, Kris MG, Gralla RJ, Kelsen DP. Phase II trial of 4'epi-doxorubicin in patients with non small cell lung cancer. *Cancer Treat Rep* 1983, **67**, 591–592.
3. Joss RA, Hansen HH, Hansen M, Renards J, Rozencweig M. Phase II trial of epirubicin in advanced squamous, adeno and large cell carcinoma of the lung. *Eur J Cancer Clin Oncol* 1984, **20**, 495–499.
4. Meyers FJ, Cardiff RD, Quadro R, *et al.* Epirubicin in non oat cell lung cancer-response rates and importance of immunopathology: a Northern California Oncology Group Study. *Cancer Treat Rep* 1986, **70**, 805–806.
5. Conley BA, Homedo J, Abrams J, *et al.* Phase II trial of 4'deoxy-doxorubicin in advanced non small cell lung cancer. *Cancer Treat Rep* 1987, **71**, 861–862.
6. Feld R, Wierzbicki R, Walde D, *et al.* A phase I–II study of high dose epirubicin in advanced non-small-cell lung cancer. *J Clin Oncol* 1992, **10**, 297–303.
7. Wils J, Utnama I, Sala L, Smeets J, Riva A. Phase II study of high-dose epirubicin in non small cell lung cancer. *Eur J Cancer* 1990, **26**, 1140–1141.
8. Martoni A, Melotti B, Guaraldi M, Pannuti F. Activity of high-dose epirubicin in advanced non small cell lung cancer. *Eur J Cancer* 1991, **27**, 1231–1234.
9. Smit EF, Berendsen HH, Piers DA, Smeets J, Riva A, Postmus PE. A phase II study of high dose epirubicin in unresectable non small cell lung cancer. *Br J Cancer* 1992, **65**, 405–408.
10. Villar A, Anton E, Jimeno J, *et al.* Fractionated high dose (HD) of epirubicin (E) in adenocarcinoma of the lung (ADL). *Lung Cancer* 1991, **7** (suppl.), 122.
11. Depierre A, Lemarie E, Dabonis G, Garnier G, Jacoulet P, Dalphin JC. A phase II study of navelbine (vinorelbine) in the treatment of non small cell lung cancer. *Am J Clin Oncol* 1991, **14**, 115–119.
12. Yokoyama A, Furuse K, Niitami H. Multi-institutional phase II study of navelbine (vinorelbine) in non small cell lung cancer. *Proc Am Soc Clin Oncol* 1992, **11**, 287.
13. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
14. Kris MG, Gralla MJ, Wertheim MS *et al.* Trial of the combination of mitomycin, vindesine and cisplatin in patients with advanced non small cell lung cancer. *Cancer Treat Rep* 1986, **70**, 1091–1096.
15. Crawford J, Ozer H, Stoller R, *et al.* Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small cell lung cancer. *N Engl J Med* 1991, **315**, 164–170.

Eur J Cancer, Vol. 29A, No. 12, pp. 1731–1734, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Prognostic Value of Quality of Life Scores in a Trial of Chemotherapy With or Without Interferon in Patients with Metastatic Malignant Melanoma

Alan Coates, D. Thomson, G.R.M. McLeod, P. Hersey, P.G. Gill, I.N. Olver, R. Kefford, R.M. Lowenthal, G. Beadle and E. Walpole

In a multi-centre randomised clinical trial comparing dacarbazine (DTIC) plus recombinant interferon-alfa2a (IFN) versus DTIC alone for patients with metastatic malignant melanoma, aspects of quality of life (QL) were measured prospectively by patients using linear analogue self assessment (LASA) scales including the GLQ-8 and by doctors using Spitzer's QL Index. QL scores and performance status at the time of randomisation were available for 152 of 170 eligible patients. These scores carried significant prognostic information. In univariate analyses, Spitzer QL Index assessed by the doctor and LASA scores for physical wellbeing (PWB), mood, pain, appetite, nausea and vomiting, GLQ-8 total and overall QL were significant ($P < 0.01$) predictors of subsequent survival. QL Index and LASA scales for mood, appetite, and overall QL remained independently significant (all $P < 0.05$) in multivariate models allowing for significant prognostic factors other than QL (liver metastases and performance status). These findings closely parallel those in patients with metastatic breast cancer. They add further validity to the QL Index and LASA scores, provide the first evidence of the prognostic significance of the GLQ-8, and argue strongly for the routine assessment of QL in future therapy trials.
Eur J Cancer, Vol. 29A, No. 12, pp. 1731–1734, 1993.

INTRODUCTION

QUALITY OF LIFE (QL) is an important consideration during management of patients with metastatic malignant melanoma. Over recent years, several methods have been developed which allow reliable and valid measurement of aspects of QL affected by advanced malignancy and its treatment [1–6]. Such measures have usually been used to compare different treatments [1, 4, 7], though prognostic associations with QL scores have been reported in breast cancer [1, 8, 9] and lung cancer [10]. We now describe the prognostic associations of QL scores obtained during a multicentre randomised clinical trial comparing dacarbazine (DTIC) plus recombinant interferon-alfa2a (IFN) versus DTIC alone for patients with metastatic malignant melanoma.

PATIENTS AND METHODS

Full details of the clinical trial on which this study is based are presented elsewhere [11]. Briefly, ambulant patients with measurable metastatic melanoma unsuitable for local therapy, who had adequate liver, marrow and renal function were randomised to receive DTIC 800 mg/m^2 every 3 weeks with or

without daily subcutaneous IFN, commencing at a dose of 3×10^6 units daily for 3 days then escalating to 9×10^6 units daily. DTIC dosage was reduced to 200 mg/m^2 for the first and 400 mg/m^2 for the second cycle in patients receiving IFN.

Patient self evaluation of QL comprised 5 linear analog self assessment (LASA) scales measuring physical wellbeing, mood, pain, nausea and vomiting and appetite [3, 6], and a single LASA scale for overall QL [5]. The physician completed a QL Index questionnaire [5]. These were the same QL scales as were used in studies in advanced breast cancer [1, 9]. In addition, we used the GLQ-8, a LASA instrument designed to measure aspects of QL affected by chemotherapy [2]. The score used in analyses of LASA instruments was obtained by measurement in millimeters from the 'good' end of the line, so that scores ranged from 0 (good) to 100 (bad). In the case of the GLQ-8, the scores for all eight items were added. Scores for the QL Index ranged from 5 (best quality of life, scored as 1 on each of 5 dimensions) to 15 (worst quality of life, scored as 3 on each). Negative coefficients in multivariate regression models therefore indicate that higher scores, which described worse quality of life, were associated with shorter survival. Performance status was assessed by doctors using the 5 point UICC/ECOG scale, in which 0 denotes the best and 4 the worst performance status. In regression analyses, the performance status score was treated as a continuous variable, although in fact all but 10 patients had a score of 0 or 1.

QL scores obtained at the time of randomisation were tested as predictors of survival using the SPIDA statistical software package [12]. As was the case with metastatic breast cancer [9], several of the QL scores and other prognostic variables showed significant violation of proportional hazard assumptions [13]. Accordingly, censored linear regression [14] was chosen as the analytical model. Each QL variable was tested singly in univariate regressions, and Kaplan–Meier [15] survival curves separating patients by QL scores prepared. Multivariate censored linear regression models using a normal transformation [16] of the survival duration were examined to determine whether the QL score remained significant after allowance for non-QL prognostic factors. Age, sex, interval from primary diagnosis to metastasis, performance status and the presence of metastatic disease at various sites (skin, subcutaneous tissues, lymph nodes, lung, pleura, bone, adrenal and liver) were included in exploratory analyses. We selected the best set [17] of patient and disease variables for inclusion in these models.

Finally, an overall regression was performed allowing inclusion of more than one QL score at a time, to test the independent predictive value of different aspects of QL.

RESULTS

QL data obtained at randomisation were available for 152 (89%) of the 170 eligible patients. The study group included 104 males and 48 females. Their median age at randomisation was 51 years (range 18–74). Sites of metastatic disease included lymph node in 51%, skin or subcutaneous tissue in 50%, liver in 34%, bone in 11% and adrenal in 10%. Randomised treatment was DTIC + IFN in 79 patients and DTIC alone in 73. None of the demographic or disease features was significantly unbalanced between treatment groups. As described in detail elsewhere [11], there was no significant difference in survival duration, time to progression or tumour response rate between groups treated with DTIC + IFN or with DTIC alone. The scores recorded in each of the QL instruments are summarised in Table 1. Since these scores are arbitrary, and the range of the possible scale used for each was variable, the raw scores were standardised for analytical purposes by dividing each of the corresponding interquartile range, defined as that part of the range by scores recorded by the mid 50% of patients (Table 1). This transformation does not alter the significance of any score in regression analyses, but ensures that the magnitude of the coefficients is similar.

All the quality of life scores were significant predictors of subsequent survival in univariate analyses (Table 2). These included patient self assessment by GLQ-8 and LASA scores for physical wellbeing (PWB), mood, pain, nausea and vomiting, appetite and overall QL and doctors' assessment using the Spitzer QL Index. Representative survival curves are shown in

Table 1. Range of QL scores at randomisation

QL score	Min	LQ	Med	UQ	Max	IQR
PWB	0	5	24	46	100	41
Mood	0	5	24	47	100	42
Pain	0	2	12	38	96	36
N & V	0	0	3	24	92	24
Appetite	0	1	9	45	100	44
Uniscale	0	7	22.5	43	100	36
GLQ-8	0	51	124	229	474	178
QL Index	5	5	6	8	14	3

LQ = lower quartile (25% scored at or below this value); Med = median score; UQ = upper quartile; IQR = interquartile range (UQ - LQ). PWB = physical wellbeing; N & V = nausea and vomiting; GLQ-8 = multi-item visual analogue QL measure (see ref. 12); theoretical maximum range of scores for QL Index was 5–15; for GLQ-8 0–800; all others 0–100. For analysis, each score was normalised by dividing each patient's score by the interquartile range of the whole group for that QL endpoint.

Table 2. Prognostic significance of quality of life scores at randomisation. Univariate regressions of survival by QL

QL score	Coeff	S.E.	*P*-value	*n*
PWB	−0.220	0.068	0.001	149
Mood	−0.244	0.070	< 0.001	148
Pain	−0.190	0.067	0.004	149
N & V	−0.153	0.051	0.003	148
Appetite	−0.304	0.070	< 0.001	149
Uniscale	−0.266	0.068	< 0.001	145
GLQ-8	−0.223	0.069	0.001	135
QL Index	−0.442	0.083	< 0.001	145

Coeff = regression coefficient (per interquartile range); S.E. = standard error of the regression coefficient; *n* = number of patients contributing to model; see also abbreviations for Table 1.

Correspondence to A. Coates.
A. Coates and R. Kefford are at the Sydney Melanoma Unit, Royal Prince Alfred Hospital, Camperdown, New South Wales 2050; D. Thomson, G.R.M. McLeod, G. Beadle and E. Walpole are at the Queensland Melanoma Project; P. Hersey is at the Newcastle Melanoma Unit; P.G. Gill is at the Department of Surgery, University of Adelaide; I.N. Olver is at the Peter MacCallum Cancer Institute, Melbourne and R.M. Lowenthal is at the Haematology-Oncology Unit, Royal Hobart Hospital, Australia.
Received 20 May 1993; accepted 1 June 1993.

Fig. 1. QL Index and LASA scales for mood, appetite, and overall QL remained independently significant in multivariate censored linear regression models allowing for liver metastases and performance status, the two significant prognostic factors other than QL scores (Table 3). In the model including QL Index, performance status was no longer a significant predictor of survival, indicating that QL Index and performance status describe similar aspects of prognosis and that in this data set QL Index is a more powerful predictor of survival than performance status. The best overall subset of prognostic factors included QL Index, liver metastases and LASA score for appetite, but not performance status (Table 3).

DISCUSSION

The present study demonstrates a clear association between aspects of quality of life and duration of survival. The prognostic significance of the GLQ-8, an instrument designed to assess changes in quality of life among patients receiving chemotherapy, may be surprising, but presumably reflects the extent to which this instrument measures some fairly general QL constructs [2]. The QL variables independently predictive of survival duration were overall QL (assessed either by the patient using LASA or the physician using the Spitzer QL Index) and the self assessment of appetite. Such associations have been noted in other settings, notably in patients with advanced breast cancer [1, 3, 9] or lung cancer [10, 18, 19] and in patients receiving palliative care [20]. In the parallel study of breast cancer patients [9], the LASA score for appetite was not an independent prognostic factor, while the score for physical wellbeing, not an independent prognostic fact or in the present set, was. Caution must be exercised in interpreting differences in such regression analyses, since there is a considerable correlation between the variables, and minor variations in this correlation may dictate which variables remain in a final regression model. It seems clear that in both studies the global QL indicators are robust predictors of survival duration. The Lung Cancer Study Group used the Functional Living Index—Cancer (FLIC) a popular QL self assessment instrument [21], which has been shown to correlate with the simpler LASA instruments used by the Australian New Zealand Breast Cancer Trials Group and the International Breast Cancer Study Group [22].

Studies such as this do not distinguish between a causative and a trivial relationship between QL and survival duration. Although patient self assessment of aspects of QL provides additional prognostic information beyond that provided by recording performance status or disease extent, it may merely be that patients are better than their physicians at gauging the severity of their illness, and thus giving QL scores which predict their longevity. Even in this case, there is good reason to ensure that this information is routinely collected and used. Furthermore, physicians using the Spitzer QL Index are apparently able to gather prognostic information they do not otherwise record, emphasising the value of thinking in terms of the various dimensions of QL when attempting to assess an individual patient's expected survival.

A more interesting possibility, equally consistent with the data presented in this and other papers, would be that the patients' QL actively influences the natural history of the underlying disease. If this were the case, therapeutic interventions could be aimed at improving survival by favourably influencing aspects of QL. Such an approach would ultimately need to be tested by controlled studies of interventions targeted at improving particular aspects of QL. Spiegel *et al.* [23, 24]

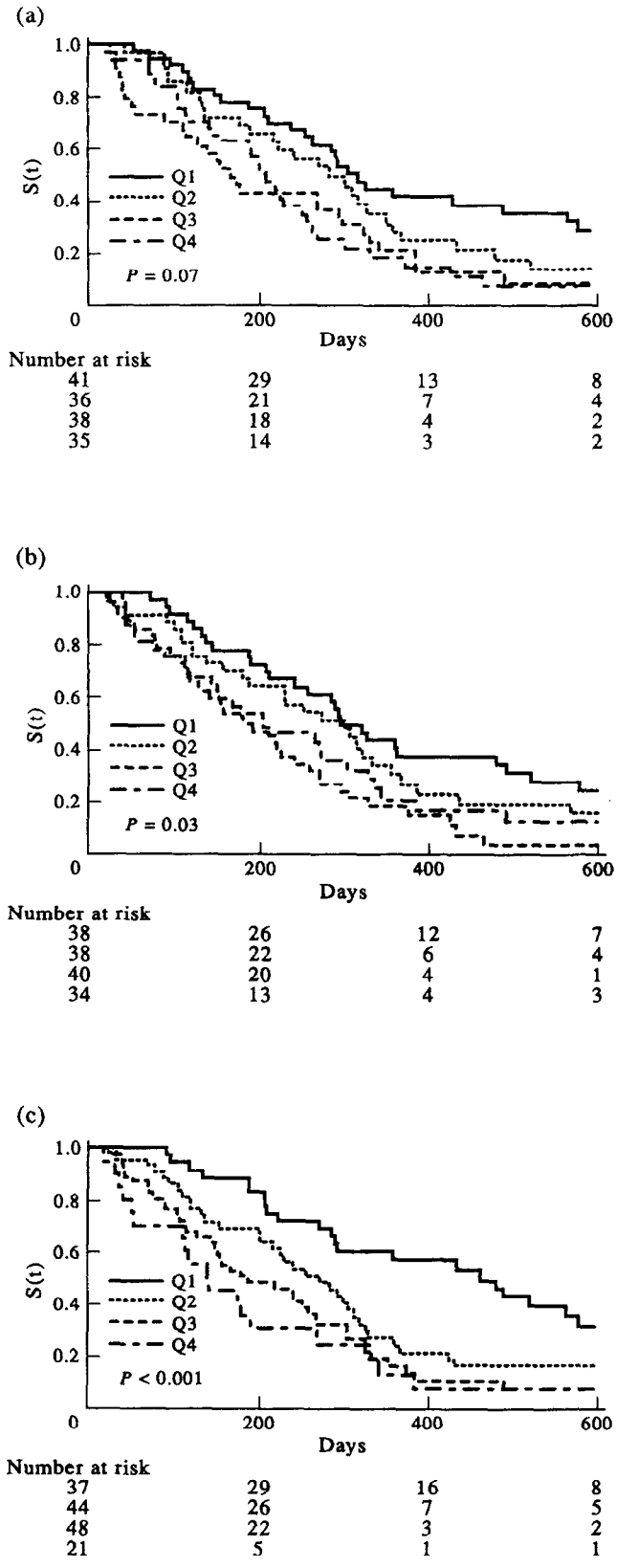

Fig. 1. Survival by QL scores. Patients were divided according to QL scores at the time of randomisation into four approximately equal quartile groups. (a) LASA physical wellbeing (single item). (b) GLQ-8 (sum of eight items). (c) QL Index (sum of five items).

Table 3. Multivariate analyses

		Coeff	S.E.	*P*-value	*n*
(a)	Significant non-QL prognostic factors				150
	Liver	−0.339	0.092	< 0.001	
	PS	−0.241	0.071	< 0.001	
(b)	QL Index added to model (a) above				144
	QL Index	−0.338	0.102	< 0.001	
	Liver	−0.291	0.091	0.001	
	PS	−0.072	0.086	0.403	
(c)	LASA appetite score added to model (a) above				148
	Appetite	−0.201	0.072	0.005	
	Liver	−0.336	0.089	< 0.001	
	PS	−0.175	0.074	0.017	
(d)	LASA global QL score added to model (a) above				144
	Global QL	−0.161	0.073	0.026	
	Liver	−0.361	0.089	< 0.001	
	PS	−0.155	0.077	0.044	
(e)	'Best' subset				141
	Liver	−0.308	0.067	< 0.001	
	Appetite	−0.168	0.081	0.038	
	QL Index	−0.313	0.090	< 0.001	

PS: performance status, ECOG scale, see also abbreviations for Table 2. Constant included in all models.

have described one such trial, which appeared to demonstrate a survival advantage for a form of group therapy intervention. Confirmation of this approach should be a priority in psychosocial research in cancer therapy. Meanwhile, the findings described here should ensure that those responsible for the palliative treatment of patients with metastatic malignancy pay attention to the quantitation of quality of life.

1. Coates A, Gebski V, Bishop JF, *et al.* for the ANZ Breast Cancer Trials Group. Improving the quality of life during chemotherapy for advanced breast cancer. A comparison of intermittent and continuous treatment strategies. *N Engl J Med* 1987, **317**, 1490–1495.
2. Coates AS, Glasziou P, McNeil DR. On the receiving end III. measurement of quality of life during cancer chemotherapy. *Ann Oncol* 1990, **1**, 213–217.
3. Priestman T, Baum M, Jones V, Forbes J. Comparative trial of endocrine versus cytotoxic treatment in advanced breast cancer. *Br Med J* 1977, **1**, 1248–1250.
4. Baum M, Priestman T, West RR, *et al.* A comparison of subjective responses in a trial comparing endocrine with cytotoxic treatment in advanced carcinoma of the breast. In Mouridsen HT, Palshof T (eds). *Breast Cancer: Experimental and Clinical Aspects*. Oxford, Pergamon Press, 1980, 223–226.
5. Spitzer WO, Dobson AJ, Hall J, *et al.* Measuring the quality of life of cancer patients, a concise QL index for use by physicians. *J Chron Dis* 1981, **34**, 585–597.
6. Coates AS, Fischer Dillenbeck C, McNeil DR, *et al.* On the receiving end — II. Linear analog self assessment (LASA) in evaluation of aspects of the quality of life of cancer patients receiving therapy. *Eur J Cancer Clin Oncol* 1983, **19**, 1633–1637.
7. Tannock IF, Boyd N, DeBoer G, *et al.* A randomized trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil chemotherapy for patients with metastatic breast cancer. *J Clin Oncol* 1988, **6**, 1377–1387.
8. Coates A, Byrne M, Bishop JF, Forbes JF. Intermittent versus continuous chemotherapy for breast cancer (letter). *N Engl J Med* 1988, **318**, 1468.
9. Coates AS, Gebski V, Signorini D, *et al.* for the Australian New Zealand Breast Cancer Trials Group. Prognostic value of quality of life scores during chemotherapy for advanced breast cancer. *J Clin Oncol* 1992, **10**, 1833–1838.
10. Ruckdeschel JC, Piantadosi S and the Lung Cancer Study Group. Quality of life assessment in lung surgery for bronchogenic carcinoma. *Theoret Surg* 1991, **6**, 201–205.
11. Thomson D, Adena M, McLeod GRC, *et al.* Interferon alpha-2a does not improve response or survival when added to dacarbazine in metastatic melanoma, results of a multi-institutional Australian randomized trial QMP8704. *Melanoma Res* 1993, **3**, 133–138,
12. Gebski V, Leung O, McNeil DR, Lunn D. *SPIDA Users Manual.* Sydney, Statistical Computing Laboratory, 1992.
13. Harrell FE, Lee K. Verifying assumptions of the proportional hazards model. *Proc SAS User Group International* 1986, **11**, 823–828.
14. Aitkin M. A note on the regression analysis of censored data. *Technometrics* 1981, **23**, 161–163.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
16. D'Agostino RB, Belanger A, D'Agostino RB Jr. A suggestion for using powerful and informative tests of normality. *Am Statistician* 1990, **44**, 316–321.
17. Lawless JF, Singhal K. Efficient screening of nonnormal regression models. *Biometrics* 1978, **34**, 318–327.
18. Ganz PA, Lee JJ, Siau J. Quality of life assessment. An independent prognostic variable for survival in lung cancer. *Cancer* 1991, **67**, 3131–3135.
19. Coates AS. Quality of Life. Prognostic implications of quality of life. *Cancer Treat Rev* 1993, **19** (Supplement A), 53–57.
20. Addington-Hall JM, MacDonald LD, Anderson HR. Can the Spitzer quality of life index help to reduce prognostic uncertainty in terminal care? *Br J Cancer* 1990, **62**, 695–699.
21. Schipper H, Clinch J, McMurray A, Levitt M. Measuring the quality of life of cancer patients, the functional living index — cancer, development and validation. *J Clin Oncol* 1984, **2**, 472–483.
22. Butow P, Coates AS, McNeil DR, Dunn S. On the receiving end IV, validation of quality of life instruments. *Ann Oncol* 1991, **2**, 597–603.
23. Spiegel D, Bloom JR, Kraemer HC, Gottheil E. The effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989, **2**, 888–891.
24. Spiegel D, Bloom JR, Kraemer HC, Gottheil E. Psychological support for cancer patients (letter). *Lancet* 1989, **2**, 1447.

Acknowledgements—This work was sponsored by Roche Products Pty. Ltd.