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Quality of life evaluation in a randomised trial of chemotherapy versus bio-chemotherapy in advanced melanoma patients

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Abstract

This study analyses the health related quality of life (HRQOL) of advanced melanoma patients, in a randomised trial comparing bio-chemotherapy (bio-CT) versus chemotherapy (CT). The trial enrolled 178 patients and the median survival was not statistically different between the two arms. HRQOL was assessed at baseline and before each cycle of therapy, using the Rotterdam Symptom Checklist (RSCL) questionnaire completed with 140 patients. At baseline, overall quality of life and psychological distress scores were the most impaired, compared with the normal population. During treatment, the difference between the two arms in the changes from baseline was statistically significant ($P=0.03$) only in the overall quality of life score, with a decrease of 6.28 points in the bio-CT arm. The mean values decreased significantly in all domains in bio-CT arm, but only in activity level and physical symptom distress scores in the CT arm. Testing HRQOL variables and prognostic clinical factors in a Cox model, only the serum level of lactic dehydrogenase, baseline overall quality of life and the physical symptom distress scores remained significant independent prognostic factors for survival. A score of less than 75 points in the overall quality of life and in the physical symptom distress domains was associated with a Hazard Ratio (HR) of 2.31 (95% Confidence Interval (CI): 1.09–4.90) and 1.92 (95% CI: 1.10–3.36), respectively.

Keywords: Quality of life; Metastatic melanoma; Rotterdam Symptom Checklist; Bio-chemotherapy; Phase III study

1. Introduction

It is becoming increasingly accepted that, in addition to traditional measurements of therapeutic outcome, such as tumour response, time to progression, disease-free and overall survival, health-related quality of life (HRQOL) assessments are essential in the clinical evaluation of patients with metastatic disease and may be more informative and useful than the clinical endpoints. HRQOL is a multidimensional instrument with physical, psychological and social domains and its measurements evaluate the overall clinical benefit that a particular treatment has to a patient. Nevertheless, only few studies have included HRQOL as an outcome measurement in metastatic melanoma [1,2]. This lack is difficult to justify considering that the patients who develop advanced melanoma have a poor prognosis [3],

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few achieve lasting remissions and the therapeutic aim remains palliation. A recent meta-analysis [4], considering 6,322 patients from 83 studies, estimated that the median survival, experienced by patients with stage IV melanoma, was 8.1 months, and the long-term survival over 2, 3 and 5 years was estimated to be 13.6, 9.7 and 2.3%, respectively.

The introduction of biological response modifiers, such as interleukin-2 (IL-2) and interferon, has for the first time raised the possibility of long-term remission, and even cure, in a proportion of patients with advanced disease [5–9]. Chemotherapy (CT) and bio-chemotherapy (bio-CT) are widely used in the management of such patients, with the hope of prolonging progression-free survival, relieving symptoms and thereby improving the HRQOL. While the addition of IL-2 and interferon alpha-2b (IFN α-2b) to chemotherapy could significantly interfere with the HRQOL of patients, HRQOL has not yet been prospectively evaluated as an outcome measurement in a randomised trial comparing CT and bio-CT. The primary objective of the trial was to evaluate whether bio-CT with cisplatin, dacarbazine, IL-2 and IFN α-2b could increase the overall survival of metastatic melanoma patients compared with CT with cisplatin and dacarbazine (DTIC) alone [10]. HRQOL evaluation was planned as a secondary objective to determine whether there was a difference between the two groups with respect to HRQOL outcomes and whether a desirable gain in survival would not be offset by a deterioration in HRQOL. Moreover, we studied whether the baseline HRQOL scores had an independent prognostic relevance in predicting overall survival.

We chose the Rotterdam Symptom Check List (RSCL) questionnaire as a measurement tool for HRQOL evaluation, since it is a well-validated self-assessment questionnaire for cancer patients, that encompasses both physical and psychological aspects of HRQOL, and an Italian version has been validated [11].

2. Patients and methods

2.1. Clinical data

Patients with advanced melanoma, who had not been previously treated with systemic chemotherapy, were enrolled in a prospective, randomised, multicentre study, in which the efficacy of cisplatin 75 mg/m^2 intravenously (i.v.), and DTIC 800 mg/m^2 i.v. every 3 weeks, and optional BCNU 100 mg/m^2 i.v., every 6 weeks, until six cycles or progression, was compared with the same chemotherapy regimen plus IL-2, 4.5 MU subcutaneously (s.c.) from days 3 to 5 and 8 to 12 and IFN α-2b, 3 MU intramuscularly (i.m.) on days 3, 5 and then three times a week. The trial was approved by the ethics committee of each participating centre, and was conducted in compliance with the Helsinki declaration. All patients gave their written informed consent.

Briefly, 178 patients were enrolled in the trial, 89 randomised to receive CT and 89 bio-CT (Fig. 1); 18 patients, 9 in each arm, also received BCNU. The main endpoint of the trial was overall survival. Two patients were excluded from the analysis of the primary endpoint since they were not eligible (wrong diagnosis for liver metastasis), but were still considered in the present study because they had received therapy. To date, the median time to progression is quite similar between the two treatment arms: 3.6 months for bio-CT and 3 months for CT, and the median survival is 11 months for bio-CT and 9.5 months for CT (Hazard Ratio (HR) = 0.89, $P = 0.51$). Toxicity, scored according to the World Health Organization (WHO) criteria, was mild and no differences were observed between the two arms, except for an almost 5-fold increase in the incidence of anaemia in the bio-CT arm.

2.2. HRQOL measurement

HRQOL was considered to be a mandatory part of the protocol.

HRQOL status was assessed by a self-report questionnaire, RSCL, which has previously been shown to be reliable and a valid instrument in the evaluation of patients treated with chemotherapy [11,12].

The RSCL questionnaire was given to the patient for completion prior to the first cycle of chemotherapy (baseline assessment), and subsequently just before each successive cycle of chemotherapy for all patients. The

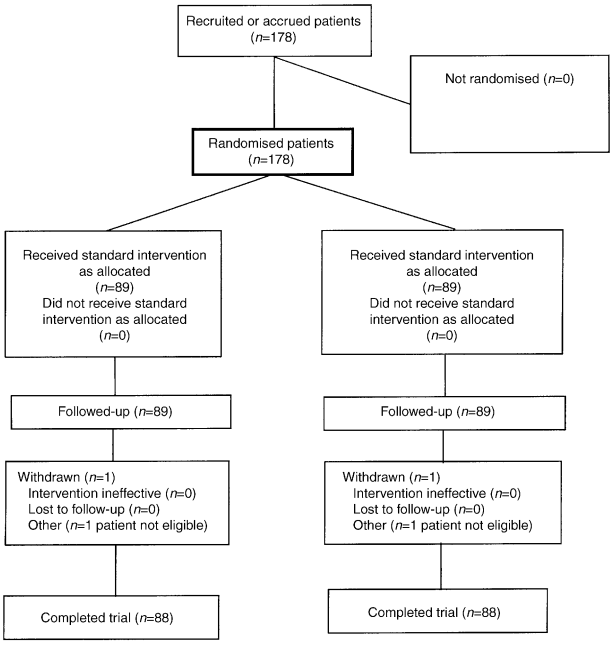

Fig. 1. Flow chart of the progress of patients through the trial (adapted from [25].

HRQOL evaluation was not planned after disease progression or during the follow-up period.

The RSCL questionnaire contains 39 items grouped into four domains: the physical symptom distress scale referring to different physical symptoms (23 items), the psychological distress scale (7 items), the activity level scale, regarding functional status (8 items) and the overall quality of life scale (1 item) [12]. The responses are given on a four-point Likert-type scale. For physical symptom and psychological distress, responses range from 'not at all' to 'very much'; for the activity level scale responses range from 'unable' to 'without help'; the overall quality of life answers range from 'excellent' to 'extremely poor' [12].

A time frame was defined in order to establish the acceptable questionnaires at each administration: 10 days before the start of treatment for the baseline questionnaire and within a week before or 2 days after the start of the following treatment cycles, for those thereafter.

Compliance was calculated as the number of forms received out of the number expected at each assessment point. To define the number of forms expected, we calculated the duration of treatment from the date of randomisation as follows: to the date of completion of six cycles of therapy if a response or stable disease was observed and to the date of progression or date of death if this occurred before the sixth cycle.

2.3. Statistical analysis

The RSCL questionnaire was scored according to recommended procedures [12]. All the domains were scored by summing their constituent items and the obtained scores were transformed into a linear scale ranging from 0 to 100, where high scores corresponded to better function and less distress.

When the individual items were missing within a scale, the missing value was substituted with the personal scale mean of the respondent, limiting this method to those cases in which the patients had answered at least half of the items in the scale [12].

A repeated measures analysis of variance [13] was performed for each of the HRQOL domains to verify whether the changes in score were different in the two treatment arms and to examine the changes over time by treatment arm. This method takes into account the longitudinal nature of the data through the correlation between assessments on the same patient.

The changes in scores were calculated by subtracting each patient's baseline score from the subsequent ones.

To study the impact on survival of HRQOL variables, the Cox proportional hazard regression model was used for both univariate and multivariate analyses. Prognostic factor analyses were performed on dichotomised baseline HRQOL scores and clinical factors such as gender, age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), site of distant metastasis, and serum level of lactic dehydrogenase (LDH). The HRQOL scores were dichotomised at 75 points that provided the partition between a complete absence from the presence of some degree of distress.

The proportional hazards assumption for each covariate included in the models was checked by plotting the estimated log cumulative hazards versus time.

Results were reported using the P value of the Wald statistic and the estimated hazard ratio with their 95% Confidence Intervals (CIs).

Data analyses were performed using the Statistical Analysis System (SAS) statistical package (SAS, release 8.00, Cary, NC, USA).

3. Results

3.1. Compliance and patients' characteristics

Between March 1997 and December 1999, 178 patients were randomised, and all were eligible for the HRQOL analysis except for 3 patients that were not included since they died before the start of treatment (2 in CT arm and 1 in bio-CT arm). One hundred and forty patients completed the baseline HRQOL questionnaire, giving a baseline completion rate of 80%.

Table 1 shows the patterns of available questionnaires. Ninety seven patients completed all of the questionnaires before dropping-out of the study due to disease progression (13 patients completed HRQOL questionnaires at all seven assessment time points). Forty three patients had some missing questionnaires; in detail, 22 patients had a monotone pattern in the completion and 21 an intermittent missing one. Fifteen patients did not have a baseline measurement and 20 patients never completed any form; these 35 patients were excluded from the analysis.

The compliance with the completion of the RSCL questionnaires is displayed in Table 2. Because of the low number of questionnaires in the sixth cycle, we did not use these data to perform the comparisons. Globally, 492 (63.6%) forms out of 773 expected were available for the longitudinal analysis. The median time of follow-up and the median time until the last completed questionnaire for the patients were 9.5 (range: 0.8–34.3) and 2.3 (range: 0–16.4) months, respectively.

Table 3 summarises the characteristics for patients who completed the baseline assessment. Patients who completed the baseline questionnaire were similar in both arms, and baseline ECOG PS was 0 in nearly 72% of patients.

3.2. Baseline HRQOL scores

Table 4 shows mean baseline scores for the domains included in the analysis, together with reference values

Table 1
Available Rotterdam Symptom Checklist (RSCL) forms and pattern of missing data

Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Frequency
*	*	*	*	*	*	*	13
*	*	*	*	*	*		14
*	*	*	*	*			11
*	*	*	*				15
*	*	*					26
*	*						24
*							16
*	*	*	*		*	*	1
*	*	*			*	*	1
*	*	*	*		*		1
*		*	*	*	*		1
*	*		*	*		*	1
*	*	*		*			2
*	*		*		*		2
*		*	*	*			1
*		*		*	*		1
*	*		*				1
*		*	*				3
*		*		*			1
*			*	*			1
*		*					4
	*	*	*	*	*	*	2
	*	*	*	*	*		1
	*	*	*	*			1
	*	*	*				2
	*	*					5
	*						1
		*	*	*	*	*	1
		*	*	*	*		2

for the normal population, from the original Dutch validation studies [12]. No differences were observed in the four domains between the two treatment arms. As a whole, the baseline measurements showed a good activity level (mean score equal to 91.8 ± 17.5) with a minimal physical symptom distress (mean score equal to 87.8 ± 11.2). Instead, the psychological distress (mean score equal to 69.0 ± 20.6) and the overall quality of life (mean score equal to 68.2 ± 15.2) were slightly more impaired.

3.3. Changes in HRQOL during the treatment

The mean changes from baseline for the four HRQOL scores were investigated for the period from randomisation to the end of the fifth cycle (Fig. 2). Repeated measures analysis of variance revealed a statistically significant difference between the two arms in the overall quality of life score ($P = 0.03$) with a decrease of 6.28 points in the bio-CT arm. There was no significant difference in the activity level ($P = 0.20$), physical symptom distress ($P = 0.08$) and psychological distress ($P = 0.25$) between the two arms, even if the mean values were always slightly inferior in the bio-CT arm (differences of 3.64 points in the activity level, 3.07 points in physical symptom distress and 3.69 points in psychological distress scores).

During the treatment, the mean values decreased significantly in all domains in the bio-CT arm (overall quality of life: $P < 0.001$, activity level: $P < 0.001$, physical symptom distress: $P < 0.001$, psychological distress: $P = 0.04$), and the most important reduction was observed in the activity level (10.49 points; CI: 6.43–14.55), whereas in the CT arm, the decrease was significant only for the activity level and the physical symptom distress ($P < 0.001$).

4. Prognostic factors for survival

4.1. Univariate analysis

Results of the univariate survival analysis for each of the variables under study are reported in Table 5.

Concerning the clinical variables, poor survival was associated with ECOG PS 1 + 2, and abnormal serum LDH level. The overall quality of life and the activity level scores were not well distributed with respect to the cut-off point representing the presence or absence of distress, but they were associated with large differences in survival ($P = 0.007$, $P = 0.036$, respectively). For the physical symptom distress score, there was an advantage for patients above the cut-off point, with a median survival of about 11 months versus roughly 5.4 months, but this difference did not reach the statistical significance ($P = 0.31$). The psychological distress score was not statistically significant. No major violations of the proportionality assumption are likely to be present for any of the variables studied.

4.2. Multivariate analysis

Clinical factors were entered first to find the prognostic multivariate model. The Cox model retained only

Table 2
Compliance with completion of questionnaires for each treatment arm

Form	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
CT							
Expected	87	87	84	55	46	30	26
Received (%)	71 (82)	61 (70)	49 (58)	35 (64)	25 (54)	16 (53)	6 (23)
Bio-CT							
Expected	88	88	78	50	46	34	31
Received (%)	69 (78)	51 (58)	46 (59)	30 (60)	21 (47)	18 (53)	10 (32)

Table 3
Characteristics of patients with baseline Health-related Quality of Life (HRQOL) questionnaires

	CT *N* (%)	Bio-CT *N* (%)
Patients	71	69
Gender		
Male	45 (63)	40 (58)
Female	26 (37)	29 (42)
Age (years)		
Median (range)	60 (27–76)	56 (25–73)
ECOG Performance Status		
0	51 (72)	50 (72)
1 + 2	20 (28)	19 (28)
Site of primary melanoma		
Head and neck	14 (20)	14 (20)
Body	29 (41)	31 (45)
Arms	26 (37)	23 (33)
Not referred	2 (3)	1 (1)
Site of distant metastases		
Other visceral sites	49 (69)	53 (77)
Soft tissue and lfn (Lymph nodes)	22 (31)	16 (23)
Serum LDH		
Normal	47 (66)	50 (72)
Abnormal	24 (34)	19 (28)

N, number; CT, chemotherapy; bio-CT, bio-chemotherapy; ECOG, Eastern Cooperative Oncology Group; LDH, lactic dehydrogenase.

Table 4
Baseline RSCL scores with baseline reference values for comparison

HRQOL scores	Mean value ± S.D.	Reference mean values[a]
Overall quality of life	68.2 ± 15.2	78.8 ± 83.7
CT (68 pts)	66.2 ± 12.2	
BioCT (66 pts)	70.2 ± 17.7	
Activity level score	91.8 ± 17.5	
CT (68 pts)	93.0 ± 17.4	
BioCT (68 pts)	90.7 ± 17.6	
Psychological distress	69.0 ± 20.6	83.0 ± 18.1
CT (68 pts)	67.4 ± 20.0	
BioCT (68 pts)	70.7 ± 21.1	
Physical symptom distress	87.8 ± 11.2	90.1 ± 9.0
CT (69 pts)	87.6 ± 11.0	
BioCT (68 pts)	88.0 ± 11.6	

S.D., standard deviation; pts, patients.
[a] According to the Original Dutch validation Studies: random sample from general population [12].

one factor: serum LDH level ($P < 0.001$). Factors that did not reach the statistical significance were: age, gender, ECOG PS and site of distant metastases. The HRQOL variables were added to serum LDH level to obtain the final multivariate model. Overall quality of life domain and physical symptom distress domain remained significant independent prognostic factors in the final model. Results are reported in Table 6. A score below the 75 cut-off point for the overall quality of life domain was associated with a hazard ratio of 2.31 (95% CI 1.09–4.90); a score below the 75 cut-off point of physical symptom distress domain was associated with a hazard ratio of 1.92 (95% CI 1.10–3.36).

5. Discussion

This is the first study of HRQOL in patients with metastatic melanoma treated with bio-CT.

Chemotherapy for metastatic melanoma has a modest activity and its efficacy has yet to be proven, therefore achieving an improvement in HRQOL could be an

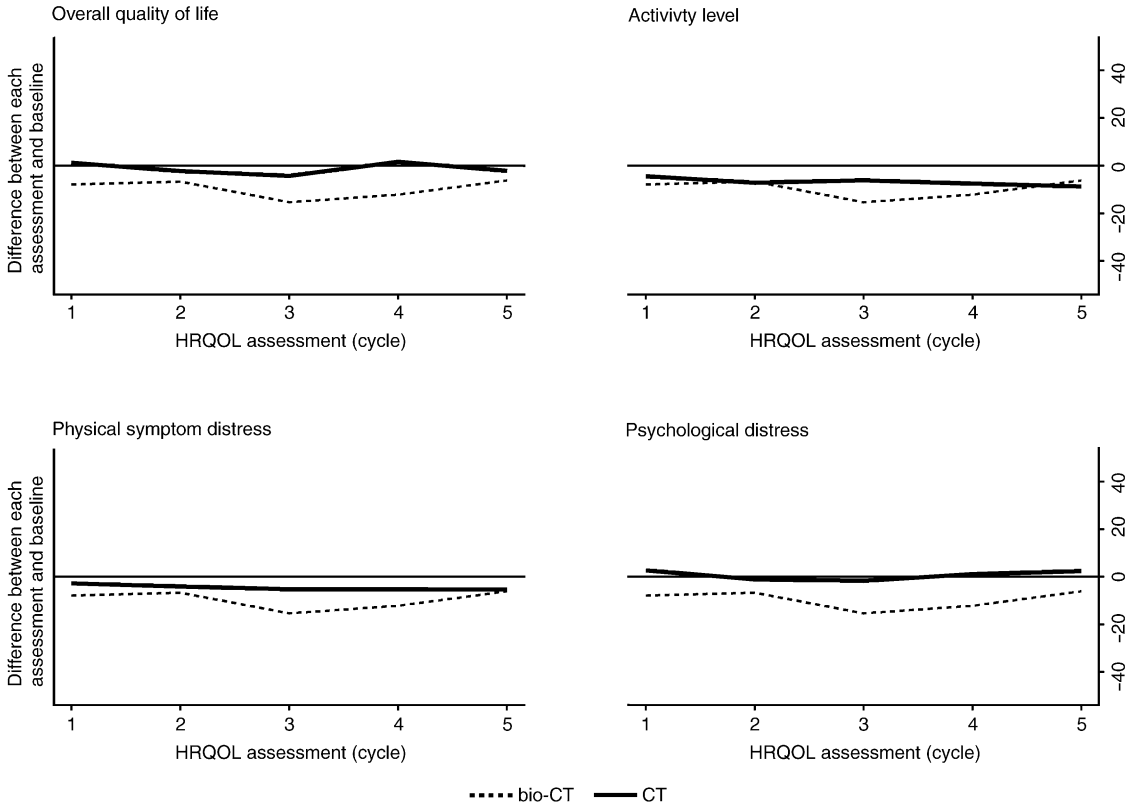

Fig. 2. Mean values of changes in score between the baseline and each successive assessment.

important benefit to patients. Since HRQOL measurement encompasses an assessment of functioning ability and toxicity from therapy, the outcomes are useful in determining the overall value of therapy from the patient's perspective and could allow a more balanced and conscious assessment of the choice of treatment.

The evaluation of the impact of bio-CT on HRQOL outcome is even more important, since a survival benefit has not yet been clearly confirmed by our [10] or other [9,14,15] randomised trials, while reported toxicity is considerable.

The treatment may improve HRQOL in some domains, but this benefit could be counterbalanced by deterioration in others as a result of side-effects of treatment.

Due to poor compliance in the completion of questionnaires in our study, the results should be considered with caution. Anyway, we feel that important information for the management of patients with advanced melanoma may be obtained, even if further studies are necessary to confirm these results.

Our study determined that a high proportion of metastatic melanoma patients have, at diagnosis, a high activity level score. This finding was expected, since more than 70% had a good performance status. In spite of this, these patients experienced a high psychological distress score (mean value <70 points) and this distress seemed to affect the overall quality of life score (mean value <70 points). Other studies [16–18] on melanoma patients, found that increasing distress was associated with an impaired functioning in a variety of areas, including physical and social, with a significantly worse evaluation of current and future personal health.

The phase III clinical trial (from which the HRQOL data reported here were collected) showed a slight, and not significant, increase in overall survival, with a similar response rate, time to progression, and toxicity in patients treated with bio-CT compared with those given CT alone [10]. Despite this, the overall quality of life score was significantly worse in the bio-CT arm. Furthermore, the analysis of longitudinal changes from baseline HRQOL scores, showed a statistically significant deterioration in all the four domains in the bio-CT arm, and this effect was worse and more extensive than that experienced by patients in the CT arm, who had a significant reduction only in the scores of the activity level and the physical symptom distress. It is expected that HRQOL should improve when there is an effective antitumour treatment, that results in a decrease of tumour-related symptoms. On the contrary, a worsening is expected when the toxicity of the treatment abrogates the benefits of tumour reduction or when the treatment is ineffective and the tumour-related symptoms rapidly increase.

The greater deterioration observed in the activity level domain in bio-CT arm was neither expected by the

Table 5
Univariate prognostic factor analysis for survival

Variable	Events/*n*	Median survivals (days)	HR (95% CI)	*P* value
Age				
⩽Median	49/70	307	1	
>Median	55/70	336	0.99 (0.67–1.46)	0.95
Gender				
M	64/85	290	1	
F	40/55	373	0.77 (0.51–1.15)	0.19
ECOG Performance Status				
0	70/101	360	1	
1+2	34/39	237	1.8 (1.19–2.73)	0.005
Site of distant metastases				
Viscera±others	79/102	290	1	
Soft tissues and lfn	25/38	418	0.8 (0.51–1.26)	0.34
Serum LDH				
Normal	65/97	418	1	
Abnormal	39/43	165	3.09 (2.05–4.05)	<0.0001
Overall quality of life				
>75	8/17	561	1	
⩽75	94/117	290	2.78 (1.32–5.88)	0.007
Activity level distress				
>75	85/120	346	1	
⩽75	16/16	250	1.79 (1.04–3.03)	0.036
Physical symptom distress				
>75	85/117	336	1	
⩽75	17/20	165	1.32 (0.77–2.22)	0.31
Psychological distress				
>75	42/62	363	1	
⩽75	59/74	282	1.4 (0.94–2.08)	0.097

HZ, Hazard Ratio; M, Male; F, female.

Table 6
The final multivariate model

Variables	HR (95% CI)	*P* value
Serum LDH level (abnormal versus normal)	3.20 (2.07–4.97)	<0.0001
Overall quality of life (⩽75 versus >75)	2.31 (1.09–4.90)	0.029
Physical symptom distress (⩽75 versus >75)	1.92 (1.10–3.36)	0.022

clinical recorded toxicity (WHO criteria), which was mild, nor by a different rate of failure or time to failure [10].

A possible relationship between the disease progression and the deterioration of HRQOL scores could not be ruled out, due to the low number of responding patients (37 only); however, this relationship would not explain the difference between the two arms. Moreover, it appears unlikely that the effect of treatment on the quality of life was confused and/or worsened by the disease progression since patients who progressed did not complete HRQOL questionnaires and were not accounted for.

Another important finding of this study was the prognostic value of the baseline overall quality of life and physical symptom distress scores which were more discriminative and informative than ECOG PS, gender, age, and site of metastases in the prediction of clinical outcome. In fact, we found that the presence of all the positive categories of prognostic factors (normal serum LDH level, overall quality of life score and physical symptom distress score above the cut-off point of 75) predicted a median survival of 18.4 months versus 4.2 months for patients with all of the negative categories. The relationship between higher baseline overall quality of life scores, and survival was previously reported by Butow and colleagues [19] and by Coates and colleagues [2] in melanoma patients, by Curran and colleagues[20] and by Kramer and colleagues [21] in advanced breast cancer, and by Maisey and colleagues in advanced colorectal cancer [22]. As stressed by Osoba and colleagues, [23] it would seem that patients with metastatic cancer are better judges of their health as expressed in HRQOL scores than are performance status scores, physical examination, or site of metastatic spreading.

Moreover, this relationship is intriguing and would reflect an early perception, by the patient, of clinical fail-

ure. How and whether this concern could influence the clinical outcome, deserves to be specifically explored.

A better understanding of the relationship between psychological distress, overall quality of life, survival, and a prospective evaluation of whether a structured psychological intervention is able to modify, positively, this finding is worthwhile. Interventions, aimed at changing levels of psychological distress, could be associated with changes in other variables and this could be translated into a clinical benefit as suggested by the study of Fawzy and colleagues [24].

In light of these results, we believe that all future trials on bio-CT, in melanoma, should include an HRQOL evaluation. Bio-CT seemed to prolong survival in phase II trials; however, such an effect has not been confirmed in randomised trials. Moreover, even if this effect exists, it may be counterbalanced by a greater worsening of the HRQOL, as shown in our study.

The overall quality of life score, the physical symptom distress score, and the serum LDH level were confirmed as independent prognostic factors in patients with metastatic melanoma. In future trials, it could be of interest to evaluate whether a planned psychological intervention is able to improve the HRQOL and, thereby, modify the prognosis of patients with advanced melanoma.

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