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QUALITY OF LIFE EVALUATION BY THE EORTC QUESTIONNAIRE TECHNIQUE IN PATIENTS WITH GENERALIZED MALIGNANT MELANOMA ON CHEMOTHERAPY

VALGERDUR SIGURDARDÓTTIR, CHRISTINA BOLUND AND MARIANNE SULLIVAN

A longitudinal quality of life (QOL) study was performed on patients with advanced melanoma during chemotherapy. The purpose was to describe QOL in this palliative context and to compare the clinical outcome variables and patients' self-assessed QOL. QOL was assessed by the EORTC core questionnaire technique (QLQ-C36), a study-specific melanoma (MM) module and the Hospital Anxiety and Depression (HAD) scale. The questionnaires displayed good psychometric qualities and the technique proved to be applicable in this longitudinal study of severely ill patients. Only six patients, out of 95 in total, complied with the full one-year study. Drop-outs occurred early in the course of treatment, most of them due to progressive disease or death. Pretreatment, patients reported a low level of dysfunction and symptom burden but 9 weeks later they exhibited significant deterioration in all QOL measurements, with the exception of pain and emotional functioning. The mean duration of response was short and there was considerable observed treatment-related toxicity. However, no correlation was found between physician-rated clinical outcome variables and QOL measurements, except for neuropathy. Our results are in accordance with earlier data on the supplementary value of QOL measurements to define endpoints in clinical trials.

Important progress in oncology during recent decades includes the prevention and early detection of primary cutaneous malignant melanoma (1, 2). This has not been accompanied by advances in the treatment of the metastatic disease, which is still purely experimental and palliative. Aggressive combination therapies have succeeded in producing a substantial tumour response without prolongation of long-term survival (3–6). Preservation of a high quality of life (QOL) for as long as possible is therefore of utmost importance.

QOL measurements can supplement the traditional biomedical endpoints in clinical trials. The methodology has received growing interest in the medical literature lately (7–9). The Study Group on Quality of Life within the European Organization for Research and Treatment of Cancer (EORTC) has since the early 1980s developed a self-assessment core questionnaire that is multidimensional, cancer-specific and cross-culturally validated (10, 11). The interim version of the questionnaire (QLQ-C36) showed promising overall psychometric results in the first field study of lung cancer patients (10). A revised version (QLQ-C30) of the core questionnaire was later validated in a second field study of lung cancer patients (11).

The aims of the present study were 1) to assess the QOL of patients with generalized malignant melanoma during chemotherapy treatment, 2) to explore the longitudinal relationship between QOL data and clinical characteristics, 3) to compare different regimens regarding QOL outcome and 4) to test the psychometric properties of the EORTC core questionnaire and melanoma-specific module over

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From the Psychosocial Unit, Department of General Oncology, Karolinska Hospital, Stockholm (V. Sigurðardóttir, C. Bolund), and Health Care Research Unit, Department of Internal Medicine, University of Göteborg and Sahlgrenska Hospital, Göteborg (M. Sullivan), Sweden.
Correspondence to: Dr Valgerður Sigurðardóttir, Krabbameinsfélag Íslands, Skógarhlíð 8, IS-125 Reykjavík.

Table 1

Main socio-demographic and clinical characteristics of 95 patients with generalized malignant melanoma

	Study group (n = 95)	Randomized to clinical trial[a)] group 1 (n = 35)	group 2 (n = 38)	Non-randomized (n = 22)
Sex				
Male	65%	67%	66%	59%
Female	35%	33%	34%	41%
Age, years				
Median	53	47	52	65
Range	20–83	20–67	28–73	40–83
Living arrangements				
Together with partner	80%	76%	68%	86%
Employment status				
Gainful employment	64%	76%	71%	32%
Site of metastatic spread				
Cutaneous–lymph	25%	24%	37%	18%
Performance status [b)]				
0 (good)	56%	76%	79%	5%
1–2 (medium)	31%	21%	16%	54%
3–4 (low)	13%	3%	5%	41%

[a)] Seventy-three patients (77%) of the study population were randomized to the clinical trial; group 1 received dacarbazine-vindesine-cisplatin and group 2 received dacarbazine-vindesine.
[b)] Missing data from one patient. (13).

time. The main clinical hypothesis concerned the relationship between changes in performance status and observed treatment toxicity and patients' self-assessments during treatment. The second hypothesis addressed the difference between regimens regarding observed treatment side effects and patients' self-assessments. We assumed that the patients' self-assessments would deteriorate with poorer performance status and increased treatment toxicity and that the side-effects of the more aggressive therapy would be reflected in a lower QOL.

Material and Methods

Patients

As part of a continuous evaluation of chemotherapy for advanced malignant melanoma, the Swedish Melanoma Study Group in 1987 initiated a randomized clinical multicentre trial comparing two regimens, dacarbazine-vindesine and dacarbazine-vindesine-cisplatin (3, 4). From the start of the trial a QOL study was conducted in parallel at two centres. Between October 1987 and January 1991, 95 patients with a histo- or cytologically verified dissemination of malignant melanoma or a progression of an earlier metastatic disease, not suitable to surgery, were examined. The tumour progression had been confirmed within two months prior to inclusion in the clinical trial and/or QOL study. Other selection criteria of the clinical trial were: measurable or evaluable lesion (cerebral metastases no exclusion criterion); performance status (WHO) $\geqslant 2$; expected survival > 3 months; age < 75 years; a normal audiogram; blood leucocytes $\geqslant 3.5 \times 10^9/l$; platelet count $\geqslant 100 \times 10^9/l$ and serum creatinine < 125 mmol/l. Sixty-five randomized patients were recruited at the Department of General Oncology, Karolinska Hospital, Stockholm, and 8 patients at the Department of Surgery, Sahlgrenska Hospital, Göteborg. An unbroken sequence of 22 patients, not eligible for the randomized study, at the Department of General Oncology, Karolinska Hospital were also included. Non-eligibility was due to a prior history of cancer (3), refused informed consent (3), an abnormal clinical parameter (9), too old (5), or too poor a performance status (2). All patients had to be Swedish-speaking. Details of the collection of socio-demographic and clinical data have been presented elsewhere (12). Table I summarizes the socio-demographic and clinical characteristics of the total patient group and the different treatment arms.

Treatment

The chemotherapy consisted of dacarbazine 250 mg/m^2 i.v. days 1–5 every 4 weeks and vindesine 3 mg/m^2 i.v. days 1, 8, 15 and 22, with or without cisplatin 100 mg/m^2 i.v. day 1 every 4 weeks. The non-randomized group received the dacarbazine-vindesine combination. Half of the patients received 3 courses or less of chemotherapy while about 20% received more than six courses. Patients randomized to the cisplatin regimen received a maximum of 3 cycles and in case of tumour response continued on the dacarbazine-vindesine regimen. No dose reduction was

Table 2

The number of responding patients with generalized malignant melanoma at each time-point and reasons for non-compliance with the QOL study

Time-points in weeks	Responding patients	Number of drop-outs due to			
		progression or death	declined QOL study	missed	other causes[a]
0	95 (100)[b]				
6	54 (57)	21 (22)	5	6	9
9	52 (55)	31 (33)	6	2	4
12	43 (45)	39 (41)	6	1	6
20	35 (37)	49 (52)	6	1	4
28	26 (27)	58 (61)	3	2	6
36	17 (18)	72 (76)	3	0	3
44	9 (9)	77 (81)	4	1	4
52	6 (6)	84 (88)	1	0	4

[a] Treatment at another clinic or a cessation of therapy because of a complete response or on request.

[b] Numbers within parentheses are percentages. Six participants were included after the first pretreatment analysis (12).

made for dacarbazine during the treatment period. In the second course, a 30–40% dose reduction was mostly needed for both vindesine and cisplatin. Subsequently, less than one-third of the patients received vindesine, because of neurological complications. Some patients with progressive disease accepted second-line therapy.

Clinical measurements

Clinical variables included: a) before the start of treatment: performance status, the site of metastatic spread (cutaneous, lymph nodes, lung, liver, bone, CNS and other sites) and randomization group; b) for every new cycle: performance status, tumour response, dose of each drug received and grade of treatment toxicity (alopecia, nausea/vomiting, haematological, renal, oto- and neurotoxicity); and c) number of treatment cycles, date of start and end of treatment, date of evidence for progressive disease and death, and the cause of death. Standard criteria were used for registration of performance status, response and toxicity (13), except for neuro- and ototoxicity. The neurotoxicity was described in three grades: 1) no peripheral neuropathy, 2) low-grade sensory toxicity or constipation and 3) severe sensory or motor neurotoxicity. The ototoxicity was reported either as evidence of clinical toxicity or not (protocol: DTIC + vindesine versus DTIC + vindesine + cisplatinum for advanced malignant melanoma; multicentre study–Sweden/Norway). The response at the end of each cycle and maximum toxicity during each cycle were recorded for the purpose of the QOL study. Patients were followed until the end of July 1993 regarding time to progression and death. Clinical data were obtained from the data coordinator of the multicentre clinical trial. For patients not eligible for randomization, information was collected by the author (VS).

Quality of life methodology

Three QOL instruments were used: 1) EORTC QLQ-C36, i.e. the interim version of the questionnaire (10, 12); 2) a study-specific malignant melanoma module ((MM-module); 12); and 3) the Hospital Anxiety and Depression (HAD) scale (14). The QLQ-C36 and MM-module were administered before the start of chemotherapy (baseline), on day 15 of the second course, on day 8 of the third course (9 weeks), on day 1 of the fourth course (12 weeks), and on day 1 of every second course thereafter until the treatment was discontinued. The HAD scale was given twice; before the start of chemotherapy and on day 8 of the third course of chemotherapy.

The assessment on day 15 of the second couse is placed between the second and the third cycles in order to reflect the experience of treatment but with 'minimal' treatment toxicity the previous week. There is a scheduled change in the protocol after the third chemotherapy cycle. Day 8 of the third course is thought to reflect the 'maximal' side-effects of therapy, as the assessment is made three days after completing five days of intensive chemotherapy. This time-point was chosen as the main comparative point.

The EORTC QLQ-C36 (10, 12) was employed as the basic QOL measurement. It contains 36 items, multi-item scales or single items to reflecting common symptoms reported by cancer patients and core dimensions of quality of life (12). The multi-item scales cover physical function (PF), role function (RF), fatigue (F), nausea/vomiting (NV), emotional function (EF), social function (SF) and global health/quality of life (QL). The questionnaire, its construction and response categories have been described elsewhere (10). Briefly, the items of the PF and RF scales have yes or no response categories, and the QL scale has a 1 (very poor) to 7 (excellent) response format. All other

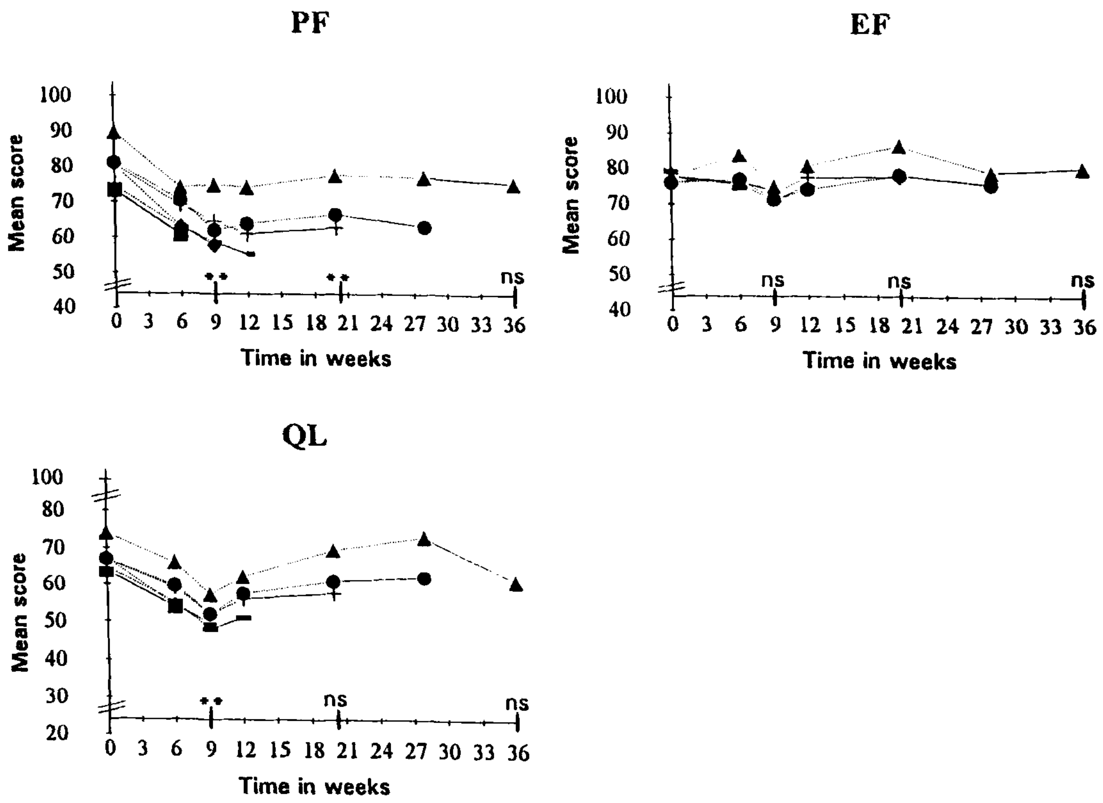

Fig. 1. Changes of patient-reported overall quality of life (QL), physical (PF) and emotional functioning (EF) during chemotherapy. The number of patients assessed at 0, 6, 9, 12, 20, 28 and 36 weeks was 95, 54, 52, 43, 35, 26 and 17 respectively. Each assessment point is compared with the preceding assessments within the same subpopulation. A higher value represents a better level of physical and emotional functioning and QL. Levels of statistical significance are indicated with $*p < 0.05$ or $**p < 0.01$; Pitman's test for three differences: 9, 20 and 36 weeks, respectively, vs. baseline. ■ 6 weeks; ◆ 9 weeks; ▬ 12 weeks; + 20 weeks; ● 28 weeks; ▲ 36 weeks.

items have four response choices from 1 'not at all' to 4 'very much'.

Reliability of the QLQ-C36 subscales. All subscales at follow-up, with the exception of RF and NV, met the criterion (0.70) for acceptable internal consistency.

Construct validity of the QLQ-C36 subscales. In order to assess the construct validity of the QLQ-C36, tests of the unidimensionality of each subscale and an inter-scale correlation analysis were adopted from the field study (10, 11). A multi-trait scaling analysis was not feasible in this limited number of patients. The principal component analysis of the PF, EF and F scales showed patterns comparable with the pretreatment results but a decreased magnitude of the item-scale correlation (12). These multi-item scales were unidimensional, with factor loadings exceeding the 0.40 level. The correlation matrix of all scales also followed a predictable pattern (data not shown), confirming the pretreatment convergent and discriminant validity of the questionnaire (10, 12).

The MM-module (12) is study-specific, developed by the author (VS) and illustrated in an earlier paper (12). It contains 13 items in addition to the core questionnaire; 11 items reflect disease-related symptoms (12) and two items address the consequences of chemotherapy. Two hypothesized scales were confirmed at baseline by principal component analysis. One scale reflected neurological symptoms (MM1) and the other pain (MM2).

Reliability of the MM-scales. At follow-up the hypothesized scales were again confirmed. Further analysis of the neurological symptom scale disclosed two unconnected components, neurological symptoms and cognitive function. The cognitive items failed to compose a scale but the neurological items confirmed a new version of the neurological symptom scale including the item representing numbness in arms or legs. Both the neurological and pain scales had high internal consistency.

Construct validity of the MM-scales. A moderate correlation (0.41) was found between the pain and SF scales. All other correlations were weak.

The Hospital Anxiety and Depression (HAD) scale (12, 14) was applied for assessment of psychological distress. Its properties are discussed elsewhere (14). The subscales of the HAD correlated with the emotional, overall quality of life and social functioning scales. Further, both the fatigue and physical functioning scales now correlated with the depression subscale.

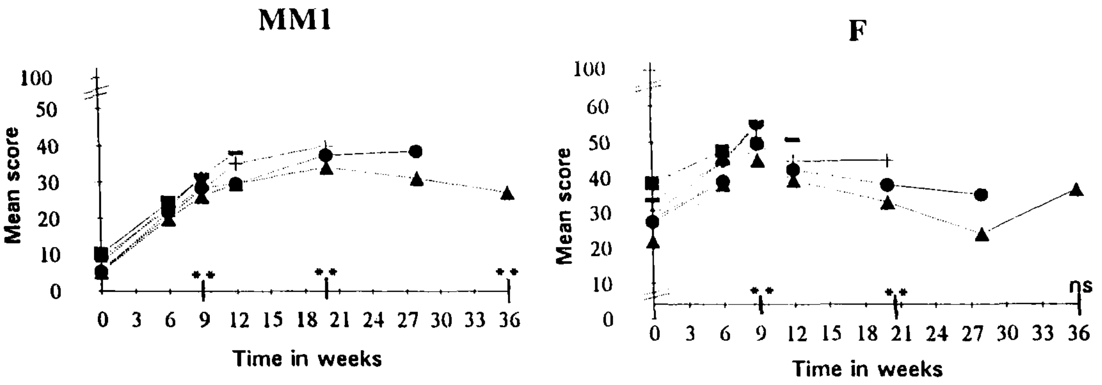

Fig. 2. Changes of patient-reported fatigue (F) and neurological symptoms (MM1) during chemotherapy. The number of patients assessed at 0, 6, 9, 12, 20, 28 and 36 weeks was 95, 54, 52, 43, 35, 26 and 17 respectively. Each assessment point is compared with the preceding assessments within the same subpopulation. A higher value of fatigue and neurological symptoms corresponds to more symptoms. Levels of statistical significance are indicated with *p < 0.05 or **p < 0.01; Pitman's test for three differences: 9, 20 and 36 weeks, respectively, vs. baseline. ■ 6 weeks; ◆ 9 weeks; ▬ 12 weeks; +20 weeks; ● 28 weeks; ▲ 36 weeks.

Procedure

Patients filled in the QOL questionnaires in the ward on the day of treatment. The research assistant was available to give help, if needed. The QOL research group was completely independent of the clinical trials group and the regular ward staff. The study was approved by the Ethical Committee of Karolinska Hospital, Stockholm.

Non-compliance

The number of respondents and the reasons for non-compliance are listed in Table 2. The vast majority of the dropouts had progressive disease or had died. Other reasons included treatment at another clinic at the time ($n = 1$), or cessation of treatment because of complete remission ($n = 5$, 4 of whom went through bone marrow transplantation), or on request ($n = 3$).

Statistical methods

All data were analysed by means of the Statistical Analysis System–SAS. Detailed descriptions of the psychometric analyses, calculation of scale scores, criteria for additive scales, establishment of reliability and construct validity of the multi-item scales have been given elsewhere (12). For ease of interpretation, all scales are linearly

Table 3

Mean score differences between 9 weeks on treatment and baseline grouped by treatment arm for performance status, QOL scales and selected items

	Study group (n = 52)	Randomized to clinical trial[a] group 1 (n = 16)	Randomized to clinical trial[a] group 2 (n = 22)	Non-randomized (n = 14)	Inter-group difference group 1/group 2
Δ Variable		Mean score difference			
Δ Performance status (PS)	0.3 (0.7)***	0.2 (0.5)	0.4 (0.7)*	0.3 (0.7)	
Δ Physical functioning (PF)	−22.4 (29.1)***	−28.6 (27.4)***	−24.4 (28.3)***	−13.3 (31.9)	
Δ Role functioning (RF)	−30.0 (46.3)**	−46.2 (30.8)**	−27.3 (45.6)	−17.8 (57.5)	
Δ Emotional functioning (EF)	−3.5 (18.0)	−4.8 (20.8)	−0.9 (15.4)	−6.4 (19.8)	
Δ Social functioning (SF)	−9.9 (25.2)**	−10.7 (26.6)	−6.8 (26.0)	−14.1 (23.4)***	
Δ Global/health quality of life (QL)	−17.3 (28.5)***	−22.0 (35.1)*	−13.2 (24.2)*	−19.2 (28.9)*	
Δ Fatigue (F)	25.8 (26.9)***	29.0 (26.1)**	30.9 (25.1)***	14.7 (29.1)*	
Δ Nausea/vomiting (NV)	11.0 (28.3)*	28.6 (23.0)**	9.1 (26.1)	−3.6 (27.9)	*
Δ Neurological symptoms (MM1)	24.7 (27.2)***	17.5 (28.3)*	38.0 (23.5)***	12.4 (24.1)	*
Δ Pain (MM2)	5.9 (28.1)	4.3 (35.0)	9.6 (28.0)	2.4 (21.9)	
Δ HADanxiety	−0.4 (3.7)	−1.2 (4.4)	−0.2 (3.4)	0.1 (3.6)	
Δ HADdepression	2.1 (4.4)**	1.0 (5.4)	1.8 (3.1)*	3.6 (5.0)*	
Δ Loss of appetite	12.7 (35.6)*	28.6 (28.8)**	6.1 (30.2)	7.1 (45.6)	*
Δ Impaired hearing	8.3 (35.1)	46.7 (35.8)**	−6.7 (22.5)	−6.1 (20.1)	**

[a] Patients randomized to the clinical trial; group 1 received dacarbazine-vindesine-cisplatin and group 2 received dacarbazine-vindesine. Levels of statistical significance are indicated with *$p \leqslant 0.05$, **$p \leqslant 0.01$ or ***$p \leqslant 0.001$; Pitman's test. Numbers in parentheses are standard deviations.

Table 4

Clinical outcome in patients with generalized malignant melanoma at baseline versus 9 weeks of chemotherapy

Clinical outcome	Pretreatment[a] n = 52		After 9 weeks n = 52	
	n[b]	%	n[b]	%
Performance status[c]				
0 (good)	30	(59)	20	(42)
1-2 (medium)	17	(33)	21	(47)
3-4 (low)	4	(8)	4	(11)
Response[c]				
No evaluation			6	(9)
Complete or partial remission			12	(27)
Stable disease			15	(37)
Progressive disease			12	(27)
Treatment toxicity[c]				
Leucocytes[d]				
Low			29	(64)
Medium			12	(28)
Severe			4	(7)
Vomiting[d]				
Low			24	(53)
Medium			14	(31)
Severe			7	(16)
Ototoxicity[e]				
No			37	(82)
Yes			8	(18)
Neuropathy[e]				
No			18	(40)
Low			18	(40)
Severe			9	(20)

[a] Pretreatment status (WHO) for participants at 9 weeks.

[b] Numbers vary due to missing data.

[c] (13).

[d] Low = WHO grade 0–1; medium = WHO grade 2; severe = WHO grade 3–4. Regarding leukocytes: grade 0 = ≥ 4.0; grade 1 = 3.0–3.9; grade 2 = 2.0–2.9; grade 3 = 1.0–1.9; grade 4 < 1.0. Regarding vomiting: grade 0 = none; grade 1 = nausea; grade 2 = transient vomiting; grade 3 = vomiting requiring therapy; grade 4 = intractable vomiting.

[e] Grade according to text, page 3.

transformed to a 0–100 scale (Table 5, Figs 1 and 2). In accordance with the modular approach of the EORTC questionnaire technique (10), probable subscales were explored where MM-module items were intended to strengthen single items in the core questionnaire (15). Hypothesized melanoma-specific scales were confirmed by principal component analysis. The significance of correlations between QOL and clinical variables was tested with Pitman's non-parametric permutation test (two-tailed test, $p < 0.05$; 17). For paired observations, a linear non-parametric permutation test was used (16). All correlations given for illustration are Pearson correlations. Significance testing of changes over time was performed by Pitman's test. Three differences were selected: 9, 20 and 36 weeks, respectively, vs. baseline (Figs 1 and 2). Analyses over time were performed on the subgroup of patients assessed at both of the comparative time-points.

Results

Clinical description

Performance status (PS) deteriorated significantly with time up to 9 weeks of follow-up (Table 3). Further analyses revealed deterioration only in the group receiving dacarbazine-vindesine within the clinical trial (Table 3). This significant deterioration was still observable at 20 weeks of follow-up (data not shown). In a substantial proportion of the patient group, tumour progression occurred early in the course of treatment. At the start of the third course (9 weeks) one-third of the patients had progressive disease while about one-quarter had a documented tumour response (see Tables 2 and 4).

The median time to progression was 12 weeks. As expected, a skewed distribution and great variance (range 1–59) were found. Six patients had progressive disease within 1.5 weeks from start of treatment and 10 lived for more than 42 weeks without evidence of progression. Of these, 5 patients were alive without evidence of progressive disease 3.3, 3.5, 3.9, 4.2 and 5.0 years, respectively, from the start of treatment. Information from 6 patients was missing due to early death ($n = 1$), emigration ($n = 1$) or no documentation found ($n = 4$). The median time to death was 29 weeks (range 1–167). All patients died of progressive disease, 5 within 3 weeks but 10 lived for over 2 years from start of treatment.

Observed haematological toxicity of severe grade was uncommon, and became even less of a problem with time. More than half of the patients had clinical symptoms of neuropathy due to treatment toxicity at 6 weeks. Despite of considerable dose reduction of neurotoxic drugs, most patients had documented problems throughout treatment. During the first 9 weeks of therapy the physicians rated severe alopecia in 25–35% of the patients and severe vomiting, neurotoxicity and clinical evidence of audiological problems in 20% (Table 4).

Relationship within and between treatment arms and QOL variables

Before treatment, patients randomized to the dacarbazine-vindesine regimen reported more frequent sweating ($p \leq 0.01$). In Table 3 the mean score differences between 9 weeks and pretreatment are presented, grouped by treatment arm. The non-randomized group experienced far less deterioration than the other two groups (Table 3). As expected, impaired hearing was significantly ($p \leqslant 0.01$) worse 9 weeks after start of treatment in group 1 receiving the ototoxic drug cisplatin (Table 3). An increase in nausea/vomiting ($p \leqslant 0.05$) and loss of appetite ($p \leqslant 0.05$) was also noted in group 1 receiving the more aggressive regimen. In contrast, neurological symptoms were more frequent ($p \leqslant 0.05$) in group 2 without cisplatin (Table 3). Only these items, reflecting side-effects, could differentiate

Table 5

Summary statistics of QOL measured by the EORTC QLQ-C36 technique and study-specific melanoma module pretreatment and after 9 weeks

		Pretreatment				After 9 weeks	
		n = 95[a]		n = 52[b]		n = 52	
	Items[c]	Mean score	(SD)	Mean score	(SD)	Mean score	(SD)
Functional scales[d]							
Physical (PF)	C1-7	72.0	(28.8)	80.2	(25.0)	58.0**	(25.2)
Role (RF)	C8-9	64.8	(40.5)	77.0	(33.8)	48.1**	(35.6)
Emotional (EF)	C23-30	75.3	(16.8)	77.2	(14.7)	73.7	(17.2)
Social (SF)	C32-33	69.3	(29.3)	70.1	(30.9)	60.6*	(27.2)
Global health/quality of life (QL)[d]	C35-36	63.7	(23.7)	67.2	(25.9)	49.5**	(21.3)
Symptom scales[e]							
Fatigue (F)	C12,13,15,21,31	39.0	(26.9)	29.3	(22.9)	54.7**	(21.7)
Nausea/Vomiting (NV)	C17-18	13.2	(20.1)	8.7	(16.9)	19.2**	(23.0)
Neurological (MM1)[f]	C22,MM40,41,46	11.3	(14.3)	7.7	(10.9)	31.2**	(27.8)
Pain (MM2)[f]	C11,MM42-43	25.8	(24.7)	20.0	(22.9)	23.8	(24.6)

[a] Pretreatment status for the total group of patients given as a reference.

[b] Pretreatment status for the subgroup of patients participating at 9 weeks.

[c] Numbers correspond to the item numbers in the questionnaires (12). On treatment, the F scale contains items C12, 13, 15 and 21 and the MM1 scale MM40, 41 and 48.

[d] A higher score represents a better level of functioning and QL on a transformed 0–100 scale.

[e] A higher score corresponds to more symptoms on a transformed 0–100 scale.

[f] MM-module subscales.

(SD) = standard deviation. Levels of statistical significance are indicated with *p < 0.05 or **p < 0.01; Pitman's test.

between treatment arms within the clinical trial. The patients in group 1 experienced a more pronounced deterioration in role functioning than the other groups but the inter-group difference was not significant (Table 3).

QOL evaluation at baseline and 9 weeks later

The subscale mean values of the QLQ-C36 and the MM-module at baseline and 9 weeks later are presented in Table 5. At pretreatment, the patients reported a relatively low symptom burden and a low level of dysfunction during the previous week. Nine weeks later there was a significant deterioration of the functional, global health/ quality of life and symptom scales except for pain and emotional functioning (Tables 3 and 5). An apparent increase of the florid symptomatology reported at baseline was also found. The ten most frequent symptoms in order of importance were: fatigue, dyspnoea, sweating, neurological symptoms, loss of appetite, constipation, nausea, bloated stomach, pain and troublesome hair loss (Tables 5 and 6). At pretreatment, the 52 participants at 9 weeks reported better QOL than the total study group (Tables 5 and 6).

The EORTC QLQ-C36 subscales

Pronounced dysfunction was observed on all items of physical functioning (PF) with the exception of the last item concerning self-care activities. At 9 weeks' follow-up, 75% were unable to do strenous work, such as moving heavy furniture, compared with 57% at baseline. Half of the patients said they were in bed or a chair and 40% stayed indoors most of the day, compared with 34% and 23%, respectively, at baseline. As might be expected on treatment, the patients experienced impaired role functioning (RF) (Tables 3 and 5).

The level of distress on emotional functioning (EF) was constant through follow-up (Tables 3 and 5). Statements reflecting depression were more often responded to than items expressing anxiety. About 40% of the patients felt that their condition or medical treatment interfered with family or social functioning (SF) at 9 weeks. By that time there was also a substantial decrease in global health/quality of life (QL). Pretreatment values showed that over 60% of the patients rated their physical condition and quality of life as 5 or more on a 7-point scale; 9 weeks later only about 30% did so. Fatigue (F) was the most common symptom on treatment as well as at baseline (Table 5). Although nausea/vomiting (NV) increased during treatment (Tables 3 and 5), only about a quarter of the patients reported nausea.

MM-module

A striking increase in the frequency of neurological symptoms (MM1) was observed during chemotherapy (Tables 3 and 5) and it was found that mostly sensoric

Table 6

Patient reports on symptoms and symptom-related problems pretreatment and after 9 weeks' follow-up

Single items from QLQ-C36 and MM-module[a]	Pretreatment		After 9 weeks
	n = 95[b] %	n = 52[c] %	n = 52 %
Dyspnoea	10	8	35**
Fever	11	4	4
Sweating	23	13	29**
Loss of appetite	20	14	23*
Constipation	14	18	23
Diarrhoea	2	2	2
Bloated stomach	16	9	23
Cutaneous swellings	16	7	17
Sleep disturbances	19	10	21**
Difficulty in concentrating	7	2	17**
Finding the right word	2	0	4
Analgesic consumption	42	27	33
Impaired hearing	9	14	15
Troublesome hair loss			53
Financial impact	6	4	10

[a] Percentages reported are for response categories 3 'quite a bit' and 4 'very much' combined (10).

[b] Pretreatment status for the total group of patients given as a reference.

[c] Pretreatment status for the subgroup of patients participating at 9 weeks.

Levels of statistical significance are indicated with *$p < 0.05$ or **$p < 0.01$; Pitman's test.

dysfunction was experienced. The mean values for pain symptoms (MM2) were stable throughout follow-up (Tables 3 and 5), as was the proportion of patients using painkillers (Table 6). At 9 weeks, one-fifth of the patients described pain either at rest or on moving, while 33% reported consumption of analgesics and all but 3 patients claimed good pain control.

Single items from the QLQ-C36 and MM-module

Table 6 discloses significant levels of patient-reported symptoms and symptom-related problems pretreatment and after the first 9 weeks of therapy. The frequency of many general symptoms increased during this period, especially dyspneoa.

The HAD-scale

On-treatment mean scores for anxiety and depression were 4.3 and 5.7, compared with 5.3 and 3.9, respectively, at baseline. Only the change of the depression subscale was significant (Table 3). Twenty-two per cent of the patients scored between 8 and 10 on the depression subscale, indicating possible clinical cases, compared with 16% on the anxiety subscale. The comparable values for probable clinical cases (scores > 10) were 12% and 6%, respectively.

Long-term follow-up

At 20 weeks there was still significant deterioration of physical functioning, fatigue and neurological symptoms, (see Figs 1 and 2). However, overall quality of life had returned to pretreatment values. The emotional and social functioning and pain were unchanged through follow-up but the patients became more restricted in working or doing household chores. Reports of nausea and impaired hearing dropped abruptly after the third and fourth courses as expected (most patients continued with dacarbazine only) and fever diminished over time. Other symptoms such as dyspnoea, sweating and difficulties in concentrating increased in frequency (data not shown).

Relationship between clinical outcome and QOL variables

Changes in performance status (pretreatment–9 weeks difference) did not correlate with any changes of the QOL subscales and single items. No correlation was found between clinical outcome variables at 9 weeks and QOL measurements, except for neurotoxicity (0.62).

Discussion

In the present study, we followed patients with generalized malignant melanoma throughout chemotherapy. These patients are uncommon at most oncology departments so multicentre studies are preferred. For this reason we chose to participate in a randomized clinical multicentre trial. Owing to feasibility aspects, however, all the participating centres of the clinical trial were not incorporated in this QOL study. As the design was complicated and required a multidisciplinary research team, it was decided at study start to involve only two centres. Thus, clinical results as a response to treatment, time to progression or death and treatment toxicity described in this paper are only interpretable in relation to our QOL data and do not represent the outcome of the clinical trial as a whole.

Two-thirds of our study population was also incorporated into the multicentre clinical trial. Most of the randomized patients (65 out of 73) accounted for 80% of accrued patients at the bigger clinic during the study period (The Swedish Melanoma Study Group). We consider the data collection representative and argue for clinical validity of our results.

Only 6 patients, out of 95 in total, complied with the full one-year QOL study. Dropouts occurred early in the course of treatment and the vast majority were due to progressive disease or death – an expected result reflecting the natural course of disseminated disease. Patients dropped out or stopped treatment earlier and faster than in comparable studies on lung cancer, advanced breast cancer and metastatic colorectal cancer (10, 11, 17–20). Despite meticulous monitoring, an additional 5–20% of the patients at each time-point were missed. They either discontinued treatment, declined participation in the QOL study, were receiving treatment elsewhere or were overlooked by the research group. These problems are certainly common in QOL research on severely ill patients but are seldom published in detail (21, 22). Our study showed that, given the resources, the QOL questionnaire technique is applicable in a group of severely ill patients in a longitudinal study.

The psychometric properties of the QLQ-C36 and the MM-module at follow-up were analyzed in accordance with to the rules and standards of the EORTC Study Group on Quality of Life (10, 11). As in our pretreatment analysis of the QLQ-C36, confirmatory results of hypothesized scale structures were attained, with the exception of those for role functioning and nausea/vomiting. (10–12, 17). They showed low-scale reliability pretreatment and neither met the standards for scale construction at follow-up. Psychometric problems of two-item scales have been described, often indicating the need of a minimum of three items to construct a scale (10, 11, 17, 23). As expected, during treatment the inter-scale correlation decreased in strength because of the smaller size of our study group. The follow-up analysis supported the hypothesized scales of the MM-module. The need to revise the neurological symptom scale on treatment reflected a strong treatment-related effect.

Our pretreatment results disclosed a relatively low symptom burden, good physical and social functioning, moderate psychological distress (mainly anxiety) and a high overall QL during the past week. Fatigue and pain were the most frequent symptoms reported (12). Nine weeks later there was a significant deterioration in performance status and one-third of the study population already had documented progressive disease or had died an early death. The observed treatment toxicity was considerable during the first 9 weeks of chemotherapy, with 60% of the patients exhibiting clinical evidence of neuropathy. Severe vomiting, oto- and neurotoxicity were noted in 20% and haematological toxicity in 10% of the patients. A substantial dose reduction was needed early in the course of treatment, whereupon haematological toxicity and nausea/vomiting became less of a problem. Objective documentation of severe alopecia remained stable throughout treatment while neuropathy continued as an increasing clinical problem.

The median time to progression and death was 3 and 7 months respectively, reflecting the short duration of response in this context, verified by others (3–6). The wide variation and skewed distribution of the response duration and survival are well known from the natural history of generalized melanoma and may indeed have very little to do with current treatment. Our data also confirmed that patients with lower levels of dysfunction were more prone to respond to treatment and continued on it for a longer period of time.

The patients' self-assessments described even more dramatic changes and a more complex and diversified scenario. They reported a significant deterioration on all functional scales, the overall QL scale and symptom scales except for pain and emotional functioning. The single-item symptom questions also disclosed a marked increase in symptom burden. Fatigue was the most frequent symptom, followed by dyspnoea, neurological symptoms, sweating, loss of appetite and pain. This is a much more pronounced and rapid deterioration than reported from comparable studies of other patient groups with advanced cancer (11, 17, 19-21). As might be expected, depression accompanied the somatic deterioration of our patients, a connection observed by others (24). On the whole, psychological distress continued to be quite moderate on treatment (12, 25–26) and neither changes in performance status nor increased treatment-related symptoms were reflected in the emotional functioning at 2 or 5 months. Others have mentioned that treatment-related toxicity seems to be better accepted than disease-related symptoms (27). Our results might support this.

A more favourable result is reflected in adequate supportive care; pain was kept under control, no increase in vomiting was observed during therapy and only a quarter of the patients reported significant levels of nausea. Antiemetic schedules are mostly directed against vomiting during therapy but nausea may last longer.

No correlation was found between physician-rated clinical outcome and patient reports, except for neurotoxicity, confirming that the physician-rated clinical outcome variables do not necessarily measure the patient's QOL. The results were in concordance with earlier data supporting the assumption of supplementary value of QOL measurements to traditional biomedical endpoints in clinical trials (8, 9, 18, 19).

Our QOL-results showed few significant differences between the two treatment arms within the clinical trial and only on items reflecting side-effects. The expectation was that the more aggressive, cisplatin-containing regimen would entail more toxicity and a lower level of overall quality of life. The difference, if any, may be either too small to be discovered in this limited group of patient or masked by the heavy symptomatology of the disease. The non-randomized group, although older and having had a poorer performance status in the beginning, expressed less dysfunction than both randomized groups during treatment. One can only speculate on explanations. Perhaps these patients had a strong wish for treatment and made their own decision that enabled them to benefit from treatment. As a non-treatment group is not feasible for ethical reasons, it is difficult to assess the exact burden of treatment. A number of recent QOL studies during chemotherapy for advanced symptomatic cancer indicate that aggressive regimens have a better response, similar survival rate and improved or unimpaired quality of life compared with milder regimens (18–20, 28). These results are inconsistent with the popular opinions favouring less aggressive therapies in palliative situations. For metastatic melanoma, however, effective palliative therapy is still lacking. Therefore, for melanoma, it is still questionable whether additional toxicity from aggressive chemotherapy that is unable to halt the rapid deterioration or improve the florid symptomatology of the disease can be accepted. In the search for new treatments, motivated patients will accept this risk and may benefit from the active approach. On the other hand, the response is of short duration and many patients die early in the course of treatment, reminding the clinician to pay more attention to the criteria for chemotherapy.

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