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The impact of phase I clinical trials on the quality of life of patients with cancer

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This prospective, non-randomized study was designed to evaluate the quality of life (QOL) of cancer patients receiving new cytoxic therapy. QOL was measured using a linear analog self assessment scale (LASA). Cancer patients who received a phase I agent ($n = 45$) had no significant changes in any of the individual QOL variables, overall QOL ($p = 0.77$) or performance status ($p = 0.08$) following one course of phase I therapy. However, patients who were not eligible for entry on a phase I protocol and who received supportive care ($n = 10$) experienced significant decreases in overall QOL ($p = 0.02$) and performance status ($p = 0.003$) after 1 month of follow-up. This pilot study suggests that participation in phase I trials does not adversely affect one's QOL.

Key words: Cancer, clinical trials, phase I trials, quality of life.

Introduction

Over the past decade, assessment of quality of life (QOL) has become increasingly important in the care of patients with cancer. Measuring QOL provides an additional valuable end-point for clinical investigations which previously have used only objective end-points such as toxicity, response rates, disease free interval and survival.[1–3] The goal of early drug trials is to determine the toxicities, both quantitative and qualitative, of new compounds. These trials represent one of the most important steps in the further development of new anticancer agents.[4] The need for and the potential benefit derived from these trials is well recognized.[5,6] However, concern regarding risk of toxicity with a small chance for response presents for some an ethical dilemma.[7]

To date, little is known and much has been speculated about the impact phase I trials have on the QOL of patients with cancer. A recent study conducted by Berdel *et al.*[8] compared the QOL of patients treated with new cytotoxic or endocrine treatment. The investigators concluded that neither QOL nor performance status was negatively effected by treatment on phase I protocols. Additionally, it was suggested that some positive influence may be derived through such participation. The information gained by these kinds of studies would be useful for both the patient and the health care providers considering this type of treatment.

QOL is multidimensional and difficult to define due to individual perceptions, attitudes and judgments.[1,3,9,10] The linear analog self assessment (LASA) scale has been shown to be an effective and valid instrument in evaluating subjective effects of different forms of anticancer treatment.[11–13] LASA scores have correlated with performance status, the objective parameter used to assess a patient's overall ability to perform certain physical activities.[14] It has also correlated with a patient's likelihood for an objective response to cancer treatment.[11,15]

The present study represents an attempt to evaluate the potential impact investigational therapy may have on the QOL and performance status of patients participating in phase I trials with new antineoplastic agents.

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Materials and methods

Patient selection

All patients had a confirmed histologic diagnosis of a malignancy and were refractory to all forms of known effective therapy. All patients were referred for consideration and evaluated for possible entry on a phase I protocol. A minimum life expectancy or certain performance status were not requirements for entry into this study. All patients were informed about the nature and extent of their disease, the investigational nature of the study, and signed an informed consent in accordance with federal and institutional guidelines.

Study design

While the ideal study design would be a randomization of eligible phase I patients to receive either phase I therapy or observation, the investigators felt that all patients who desired treatment should have the opportunity to participate in phase I trials. Therefore, this pilot study was designed as a non-randomized, prospective trial. When patients were referred for consideration of a phase I trial, they fell into one of three categories:

(i) Patients eligible for entry on a phase I trial who accepted and subsequently received a phase I agent, $n = 64$.
(ii) Patients eligible for entry on a phase I trial who refused treatment with the agent and subsequently received routine or supportive care, $n = 4$.
(iii) Patients considered ineligible for entry on a phase I trial secondary to some organ dysfunction and, therefore, received supportive care, $n = 28$.

The four patients in the second category who were eligible but refused phase I therapy unfortunately were lost to follow-up after returning to their referring physician. Due to the small number of patients in this group and inadequate QOL assessments completed (less than two), we did not evaluate these patients further.

Those patients who accepted and received investigational therapy were entered on one of seven phase I trials that were ongoing at our institution between 1983 and 1985. These phase I agents included echinomycin, 2-fluora-ara-AMP, tiazofurin, carbetimer, menogaril, pyritrexim and didemnin-B.

Study parameters/instruments

All patients were followed for QOL, performance status and survival.

QOL. QOL was measured using the LASA scale. This instrument is a valid and reliable measure of QOL parameters and is manageable in the clinical setting.[12,13,16] Each of the 14 variables included a 10 cm line with extreme states of the variable labeled at either end (e.g. Feeling of well being: Feel lousy, . . . , Feel great). Patients responded by marking a vertical line at any point along the 10 cm horizontal line indicating how they were feeling at the present time. The specific variables measured could be categorized under four general headings as follows:

(1) Performance
  (a) level of activity
  (b) ability to perform housework or a job
  (c) level of social activity
(2) Personal attitudes and beliefs
  (a) general well being
  (b) mood
  (c) level of anxiety
  (d) hope
(3) Symptoms
  (a) pain
  (b) nausea/vomiting
  (c) appetite
(4) Support
  (a) family support
  (b) doctors and nurses support

For those patients receiving phase I therapy, two additional variables were included to determine whether chemotherapy side effects were tolerable or intolerable, and whether the patient felt the treatment given to them was helping.

LASA scores for individual items were obtained by measuring in centimeters from the right end of the line to the patient's mark. Mean LASA scores were obtained by adding individual scores and dividing by the total number of responded items. Low LASA scores indicated the patient perceived his QOL to be poor while high scores reflected a good QOL.

Performance status (PS). PS was measured using Southwest Oncology Group criteria (scale of 0–4 with 0 being fully active without limitations and 4 being bedridden). PS was determined by the patient's primary physician.

For patients treated on a phase I protocol, the

above parameters were completed prior to initiating treatment and prior to each subsequent course (every 3–4 weeks depending on the schedule of drug administration for each phase I agent being studied). For patients receiving supportive care, QOL and PS were measured at the time they were considered ineligible to receive phase I therapy and weekly intervals.

Survival time. Survival time was defined to be the number of days from entry on the study until death.

Statistical analysis

All results were analyzed using non-parametric methods. To assess overall QOL from prestudy to the first monthly evaluation, an analysis of variance for repeated measures was utilized. Wilcoxon signed rank test evaluated the changes in QOL after two consecutive LASA scales were completed. The correlation between QOL and performance status at prestudy was assessed using Spearman's correlation coefficient. Overall survival was calculated according to the method of Kaplan and Meier[16] and compared by log-rank tests.[17] Multivariate survival analyses were performed with Cox's partially non-parametric regression model to evaluate the predictive power of various combinations of prognostic factors.[18]

Results

A total of 92 patients were entered into this study. The characteristics of patients in the phase I and supportive care groups are shown in Table 1. Patients were considered evaluable if two or more QOL evaluations (LASA scales) were completed. In the phase I group, 45 of 64 patients (70%) were evaluable, while in the supportive care group, 10 of 28 patients (36%) were considered evaluable. Reasons for patients being unevaluable and completing less than two LASAs are outlined in Table 2. Because of the marked differences in the study populations (patients eligible versus those ineligible to receive phase I therapy), there was no attempt to compare the two groups with regard to QOL, PS or survival.

Changes in QOL depicted by median LASA scores, following two consecutive evaluations are shown in Table 3. In the phase I group ($n = 45$), there was no significant change in any of the individual QOL variables after one course of phase I therapy. In the supportive care group ($n = 10$), there was a significant alteration in both appetite ($p = 0.03$) and doctors/nurses support ($p = 0.03$). Within this group of 10 patients, appetite decreased in seven patients and increased in three patients, while doctors/nurses support decreased in seven patients, increased in two patients and was without change in one patient. Although a decrease in appetite may be expected in these patients, the decline in doctors/nurses support may be due to this category of patient receiving no further treatment even though the patients were seen every week.

Table 1. Patient characteristics

Characteristics	Phase I treated	Supportive care
No. patients entered	64	28
No. evaluable patients	45	10
Male/female	54/10	25/3
Median age in years (range)	60 (31–83)	62 (45–73)
Median performance status (range)	2 (1–3)	2 (1–4)
Prior treatment	56	26
chemotherapy alone	7	3
radiotherapy alone	5	7
surgery alone	1	2
chemotherapy and radiotherapy	9	7
surgery and radiotherapy, and/or chemotherapy	34	9
none	7	2
Tumor types		
lung	21	15
colorectal	17	4
renal	8	3
head and neck	5	2
unknown primary	5	1
breast	2	1
sarcoma	2	—
pancreatic	2	—
melanoma	1	1
prostate	1	1
Median no. phase I agents received (range)	1 (1–4)	NA
Median no. courses received (range)	2 (1–12)	NA

Table 2. Unevaluable patients

	Phase I ($n = 19$)	Supportive care ($n = 18$)
Progressive illness/ weakness	12	11
Death	5	6
Refused participation	2	1

Table 3. Changes in quality of life (LASA scores)[a] after two consecutive evaluations

	Phase I group ($n = 45$)			Supportive care group ($n = 10$)		
	Time 1	Time 2	(p-value)	Time 1	Time 2	(p-value)
Performance						
level of activity	6.70	7.60	(0.22)	8.25	9.10	(0.20)
ability to work	8.40	9.00	(0.47)	9.65	9.85	(0.84)
social activity	8.50	8.50	(0.72)	8.40	9.90	(0.28)
Performance attitudes/beliefs						
hope	0.50	0.90	(0.41)	2.90	4.75	(0.07)
level of anxiety	3.40	3.40	(0.99)	8.25	9.10	(0.20)
mood	4.20	4.30	(0.84)	6.05	7.30	(0.15)
general well being	5.00	5.40	(0.98)	6.55	7.20	(0.88)
is treatment helping?	4.25	3.95	(0.99)	NA	NA	NA
Symptoms						
chemotherapy side effects	1.65	1.75	(0.99)	NA	NA	NA
nausea	1.80	1.80	(0.44)	3.50	5.20	(0.24)
pain	4.10	3.70	(0.16)	6.30	5.90	(0.44)
appetite	4.90	5.80	(0.47)	4.35	5.15	(0.03)
Support						
doctors/nurses	0.40	0.40	(0.56)	0.50	3.25	(0.03)
family	0.60	0.50	(0.22)	0.45	2.40	(0.12)

[a] LASA scores: 0 = best, 10 = worst.

Overall QOL for the phase I treated group showed no significant change ($p = 0.77$) from baseline, prior to receiving a phase I agent, to the first monthly evaluation (Figure 1). The supportive care group, on the contrary, had a significant decrease in their overall QOL between the two monthly time points ($p = 0.02$). When QOL was examined in patients completing three consecutive evaluations, the number of patients evaluable in each group decreased nearly 50%, with only 29 patients being evaluable in the phase I group and four patients in the supportive care group. As would be expected, overall QOL, as measured by median LASA scores, declined in both of these groups the longer they were followed and as their disease progressed. (Phase I group: median LASA scores at Time 1 = 4.25, Time 2 = 3.89, Time 3 = 4.90; supportive care group: Time 1 = 5.91, Time 2 = 6.34, Time 3 = 6.76).

Other parameters were examined for their potential relation to QOL/LASA scores. Figure 2 demonstrates the correlation between QOL and PS at the initial or prestudy evaluation. As apparent in this scattergram, the best PS correlated with the best QOL. As PS deteriorated, so also did QOL.

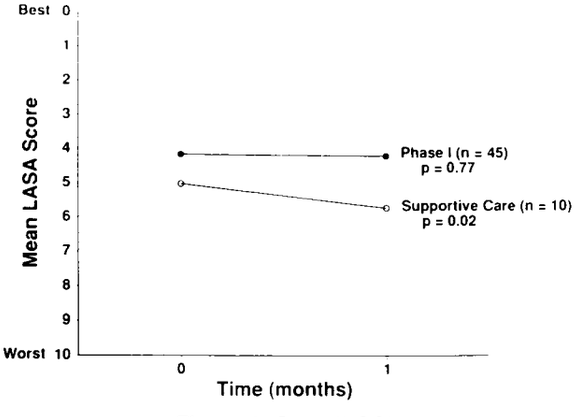

Figure 1. Overall QOL.

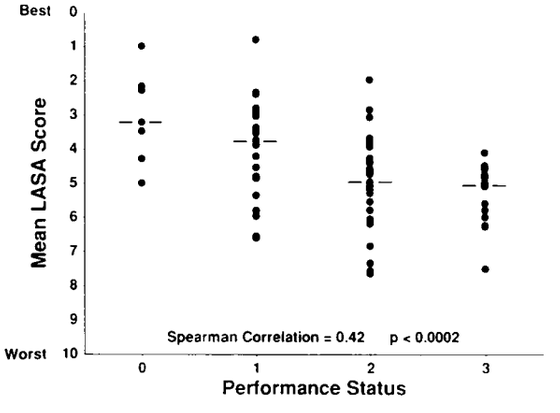

Figure 2. Correlation between QOL and performance status at prestudy evaluation.

The correlation ($r = 0.42$) between these two variables was significant ($p < 0.0002$). Mean PS was then compared for the phase I and supportive care groups for Time 1 versus Time 2. For the phase I group, there was little change from prestudy to the first monthly evaluation ($p = 0.08$). In the supportive care group, however, there was a significant decrease in performance status between these two time points ($p = 0.003$). When PS was assessed at three points (prestudy, month 1 and month 2), the number of evaluable patients in each group declined. As expected, so did the patient's overall ability to perform certain activities.

Survival was measured from time on study to death. The median survival of patients receiving phase I therapy was 4 months (range <1–23 months), and for those receiving supportive care, 1 month (range <1–7 months). A multivariate analysis was performed to determine which factors predicted for survival. Performance status was the single most important variable ($p = 0.0001$) followed by QOL/LASA scores ($p = 0.05$). Age, sex and whether the patient received a phase I treatment showed no significant prognostic value.

Discussion

Results of this prospective, non-randomized pilot study demonstrate that participation in a phase I trial does not alter one's QOL or PS following at least one course of phase I therapy. These data are similar to the findings of Berdel *et al.*,[8] which is the single previously published study addressing QOL in patients who participate in phase I trials. For patients receiving supportive care, there was a significant alteration in both appetite and doctors/nurses support with the first monthly follow-up. While a decrease in appetite may be expected, the decline in staff support was not anticipated. These findings should, therefore, heighten our awareness to patients who reach this more advanced stage of their disease and help us recognize their need for our continued support.

QOL assessment utilizing the LASA scale has potential for routine clinical use. Similar scales are currently being used in large cooperative group trials. The reliability and validity of this instrument have previously been demonstrated and, therefore, were not tested.[12,13,16] The feasibility of patients with advanced cancer completing the scale with only minimal assistance was demonstrated.

In the present study, QOL/LASA scores were significantly related to performance status. This association provides an objective contact in an otherwise subjective area and, thus, lends support to the validity of the LASA scores. In multivariate analyses, performance status and LASA scores were the only variables that predicted for survival. The correlation between the two variables and the prognostic significance of PS has been previously described.[14] Although survival time was measured, the study was not designed to evaluate the effect phase I trials have on this variable.

Inherent in trials that evaluate QOL in patients undergoing cancer treatment are limitations with regard to definition, and collection and analysis of the data. While the ideal study design would be a randomization of eligible phase I patients to receive either phase I therapy or observation, the authors did not feel this was feasible. Unfortunately, evaluation of our third category of patients (those eligible but who refused phase I treatment) was not possible due to the small number of patients entered in this group and non-compliance in completing LASA. Such a study is warranted and would permit comparative evaluations.

Conclusion

The inclusion of QOL measurements in cancer clinical trials is strongly advocated. In phase I investigations where the primary goal is toxicologic, it is anticipated that information regarding the impact of one's participation in these early trials on QOL of life would be of value. This type of information may be useful and of value to both the patient considering treatment on a phase I protocol and health care providers recommending it.

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