Quality of life as an endpoint in Phase I oncology clinical trials of novel chemotherapy drugs

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This paper examines the rationale, utility and feasibility of including quality of life as an outcome measure in Phase I trials of new applications of chemotherapy drugs. Typically Phase I trials in oncology are designed to assess safety and maximal tolerated dose; however, it is argued that when subjectively assessed, self perceived quality of life is as important as physical toxicity. The outcomes of studies that have applied quality-of-life assessment in Phase I trials are reviewed, and recommendations are made for future research based on both methodologic and practical considerations.

Expert Rev. Pharmacoeconomics Outcomes Res. 5(5), xxx–xxx (2005)

CONTENTS

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KEYWORDS:
health-related quality of life, oncology clinical trials, Phase I trials, quality of life

This review paper is focused on the issue of quality-of-life (QOL) assessment in Phase I clinical trials of new cancer chemotherapy drugs. First, the scope and methods of the literature review will be specified, followed by a discussion of QOL: its definition, measurement issues and common measures of QOL in oncology. This is followed by a review of Phase I trials in general, their objectives and usual outcomes. The issue of why it is important to measure QOL in Phase I cancer trials is addressed, followed by a systematic review of studies that have assessed QOL as an outcome in Phase I trials. Methodologic concerns related to QOL measurement in advanced cancer patients are then addressed. The review concludes with a summary, expert commentary including recommendations for clinical practice, and five-year view.

Scope & methods

The scope of the review has been limited to two types of studies:

- Those that discuss the conceptual issues around QOL assessment in Phase I trials, and assess QOL and/or attitudes towards QOL testing in patients before participation in trials
- Those that assess QOL as an endpoint or outcome in Phase I trials, and report QOL measurements for at least two time points

The latter studies are exhaustively summarized in TABLE 2, while the former are used throughout the paper selectively to make points where appropriate. The following criteria were utilized when selecting papers to include in the second category:

- Investigation of a chemotherapy drug regimen or combined regimen in a Phase I human trial with cancer patients as subjects
- Use of a standardized QOL outcome measure

Therefore, studies that were addressing new radiation therapy regimens or novel immunotherapy drugs were excluded, as were studies that assessed QOL with performance status only, or self-created unvalidated QOL measures.

Papers were found using a comprehensive search of the following databases: EMBASE, HealthSTAR, MEDLINE, PsycINFO and PubMed. Select keywords, their abbreviations and all possible combinations of keywords were searched. Quality of life was searched for as a keyword and a subject heading and with the abbreviations QOL and QL. Phase I clinical trial(s) was searched for as a keyword and subject heading and using the numeral I and the number 1. Chemotherapy and cancer/neoplasms were both searched for as keywords and subject headings in the appropriate databases. A snowball technique of identifying other applicable

10.1586/14737167.5.5.xxx

ISSN 1473-7167

papers from the reference lists of found articles was also used. Applicable articles were limited to those that were written or translated into English.

Literature review

Defining & measuring quality of life

QOL is a specific term encompassing a broad spectrum of issues, including physical, social, cognitive, spiritual, emotional and role functioning as well as psychologic symptomatology and pain. A distinction is often made between health-related QOL (HRQOL), and overall QOL, with the former focusing primarily on domains of QOL specifically believed to be directly related to one's health state. Overall, QOL measures include a more broad focus on life domains in addition to those directly related to health status. HRQOL measures are by far more commonly used in oncology than broad-based QOL measures. There are a growing number of researchers, policy makers and regulators advocating that the inclusion of patient-reported outcomes (PROs) be made mandatory for all clinical trials [1,2]. This has been referred to as the PROs movement. PROs include subjective patient experience and satisfaction as well as formal measures of HRQOL.

Common measures of HRQOL include the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 [3]. This consists of 30 self-administered items measuring six domains: physical functioning; role functioning; emotional functioning; social functioning; common physical symptoms of cancer and its treatments; financial impact; and overall perceived health status and global QOL. Similarly, the Functional Assessment of Cancer Treatment (FACT) general questionnaire uses 27 items to assess physical, social, emotional and functional wellbeing [4]. Within both of these systems, there are also disease- and treatment-specific modules, for example, for breast and prostate patients, or for those undergoing bone-marrow transplantation. Both systems have been translated into many languages, have good psychometric properties and are readily available for use at no cost. Additional commonly used measures in oncology that are not specifically designed for cancer patients include the RAND Short Form-36 (from the Medical Outcomes Study group), the Hospital Anxiety and Depression Scale (HADS), the Profile of Mood States (POMS), and others. These are summarized and referenced in TABLE 1.

As can be seen from TABLE 1, different measures may be more appropriate in certain clinical settings, depending on the constructs of interest one would like to assess, and the need for brevity. It is important when choosing a QOL measure to consider the purpose of the measurement and the specific conceptual construct that a researcher may be attempting to capture. Some measures focus more on psychologic states such as anxiety and depression, or overall distress, whereas others focus more on functional ability and activities of daily living. Therefore, these different types of QOL measures are not directly comparable with one another and are more or less appropriate for use depending on the study objectives. For example, in a Phase I trial, as described below, one must consider whether the objective is to measure detrimental effects of treatments on QOL (what the authors refer to as QOL toxicity), or to more generally characterize the experience of patients participating in such trials.

Another concept that is often used in the health economics arena combines ideas of QOL, with quantity of life, for example, assessing the impact of a new treatment in terms of healthy years of life gained, to which a specific value has been assigned. This is known as cost–utility analysis. It is the only health economic outcome that takes into account both the cost of a procedure, and factors QOL into the outcome as a measure of benefit. Typically, this metric is standardized in terms of quality-adjusted life years (QALYs), also known as quality-adjusted survival (QAS). The quality or value assigned to each health state is known as the utility of that state, as determined by an individual or society using a scale with anchors of zero (death) to one (perfect health). Therefore, to determine the QALY of a treatment, the total number of life-years gained from the treatment is weighted by the QOL in the resultant health state. As an example, a patient living in a health state assigned a utility value of 0.7 for a period of 10 years, would live the equivalent of 7.0 QALYs. This type of analysis has been applied in some clinical chemotherapy trials, but often in later phases, since Phase I trials do not typically set out to measure long-term benefit. It is possible, however, to compare the utility of health states arising from the implementation of different new drugs or treatment combinations in Phase I trials [5].

An additional trend in QOL measurement is to combine qualitative analysis of the patient's self perceived QOL with the quantitative measurement of these factors. A interview-based subjective measure of QOL that achieves this is called the Schedule for the Evaluation of Individual Quality of Life - Direct Weighting (SEIQOL-DW)[6]. The SEIQOL-DW is unique in QOL measurement as it elicits from patients their own self-generated list of the five most important domains of QOL, rather than asking about preset areas. After patients identify their most important domains, they rate how well each domain is currently going for them, and how important each domain is to them. Therefore, a numeric score that combines the weightings of the importance of each area with the assessment of current QOL in that area can be obtained and compared between individuals, even though nominated QOL domains may be quite different. This instrument and its predecessor, the SEIQOL [7], have been used in several published studies in oncology [8–10]. The SEIQOL-DW has been found to be acceptable and practical to use in a validation study of patients on Phase I clinical trials [10]. Patients with advanced cancer were good judges of their own QOL and were able to complete the interview with little difficulty [9].

Phase I clinical trials

The routine practice for introducing any new medication, or in this case, chemotherapy drugs, for use in clinical practice, is through the clinical trials mechanism. Well-developed procedures for establishing the efficacy of new drugs have been

Table 1. Quality of life/mood assessment instruments.

Instrument	Number of items/time	Psychometric evidence*	Comments	Ref.
Beck Depression Inventory	21/13 5 min	Good	Very commonly used in psychiatry - focus only on depressive symptoms, somatic and cognitive. Not overly responsive to change	[41]
Brief Symptom Inventory	53/18 3–7 min	Excellent	Shortened versions of the Symptom Checklist-90 family, measures overall psychopathology. Good correlation with longer scales. 10 subscales on 53-item version - 3 on 18-item version	[42,43]
Centre for Epidemiological Studies – Depression	20/10 3 min	Excellent	Good population-based assessment of diagnostic symptoms for depression	[44]
EORTC QOL Questionnaire C-30	30 5–7 min	Excellent	Used as QOL measure in all EORTC trials - translated into many languages. Functional as well as symptom scales. More emphasis on health-related QOL, less on psychological outcomes	[3]
Functional Assessment of Cancer Treatment - General Questionnaire	27 5–7 min	Excellent	Assesses physical, social, emotional and functional QOL	[4]
General Hospital Questionnaire	60/30/28/20/12 5–20 min	Excellent	Asks the patient to compare how they feel now with how they usually feel. Losing favour in oncology settings	[45]
Hospital Anxiety and Depression Scale	14 5–7 min	Excellent	Easy to complete and lots of psychometric data, including sensitivity and specificity. Often used as benchmark in validating other distress measures	[46]
Profile of Mood States	65/30/18/11 3–15 min	Good	Popular in psycho-oncology, six mood subscales, responsive to treatment changes	[47]
Rotterdam Symptom Checklist	39 5–10 min	Good	Checklist for a range of general QOL dimensions symptoms. Popular in Europe	[48]
Short Form-36	36 7–10 min	Excellent	Generic measure for use with population health surveys - eight subscales, not specific to cancer. Very popular in medical settings	[49]
Sickness Impact Profile	136 15 min	Unable to assess	12 subscales: broad range of QOL domains assessed. Can be divided into physical and psychosocial dimensions. Often used in cancer	[50]

*Psychometric evidence rated on scale: unable to assess, poor, moderate, good or excellent.
Poor: Used without determining reliability or validity.
Moderate: Reliability (internal consistency and test-retest) in one or more samples, limited validity data.
Good: Reliability and validity assessed in more than one population, evidence of concurrent and discriminant validity.
Excellent: Reliability assessed in multiple samples, large n, evidence of criterion and predictive validity.
EORTC: European Organization for Research and Treatment of Cancer; QOL: Quality of life.

elucidated by many organizations and institutions, including the US Food and Drug Administration in the Code of Federal Regulations [101]. The first step in moving from laboratory animal data and *in vitro* cell models towards applying therapeutics *in vivo* with patients is the Phase I trial. A total of 95% of patients participating in Phase I trials indicated that QOL was at least as important to them as length of life [11], yet QOL is not typically included as an outcome. Instead, the goals of the Phase I trial are generally to determine the safety and toxicity profile of a new agent (or new combination or application of already approved agents), the maximum-tolerated dose and any possible side effects. Objectives may also include identifying a

minimum biologically active dose, thus study designs almost always involve dose escalation. Pharmacokinetics and dynamics of the drug in the body may also be of interest at this phase. In cancer drug trials, a small number of patients are treated in Phase 1 trials (usually ranging from 20–80 participants). Treatment begins with very small doses (e.g., $1/10^{th}$ the LethalDose10 in the most sensitive animal species) and increases slowly across patients until the maximally tolerated dose is established through measurement of toxicity profiles [10].

Patients enrolled in Phase I cancer clinical trials are usually those with metastatic disease for whom standard therapies have failed, are contraindicated, or for whom standard therapies do not yet exist. Patients often perceive potentially higher levels of personal benefit from their participation in Phase I trials than do treating physicians [11–13]. Indeed, although the stated goals of Phase I trials are usually not to evaluate the effect of the therapeutic agent on disease status, tumor response is commonly considered an endpoint, and patients often focus on this possibility [14–16]. In one study, 85% of patients indicated they decided to participate in a Phase I trial for reasons of possible therapeutic benefit [15]. Estimates of therapeutic response for patients participating in Phase I trials of less than 5% speak against this likelihood [17–19].

Indeed, a recent review of 213 Phase I trials from 1991–2002 involving 6474 patients found only a 3.8% response rate [18]. Similarly, a study of classic Phase I oncology trials found a 4.4% overall response rate [20]. However, when these authors expanded the definition to include studies of newer, targeted agents, such as antiangiogenesis factors, vaccines and gene therapies, as well as new combinations of already approved agents, the response rate improved to 10.6% [20]. Nonetheless, despite this higher estimation of benefit, it is still far below that perceived by patients participating in these trials. Despite the patients' clear overestimation of their own personal likelihood of benefit, patients continue to feel that they are fully informed about participation in Phase I trials [16]. This discrepancy has led researchers to seriously question the ethics of Phase I trials in these potentially vulnerable patients [21–23].

Despite the focus of patients in Phase I trials on disease control, it is traditionally only in Phase II trials that endpoints include tumor response, where one goal is to determine any potential therapeutic effects. In larger-scale Phase III trials, the new indication is compared with standard treatment or current best practice in a randomized controlled design, with outcomes routinely including both disease response and QOL. Interesting, the EORTC has guidelines indicating that QOL assessment must be included in Phase III trials, but not in Phase I or II [24]. Nonetheless, there is recognized value in assessing QOL prior to the stage at which a drug is ready for Phase III [25]. Indeed, if the goal in Phase I is to measure toxicity, it may well be argued this should include the specific QOL toxicity of a treatment on function and specific symptoms such as fatigue levels, as well as the more subjective effect of potentially confounded hopes on the patient's overall life. Specific measures and techniques would need to be applied to attain each of these QOL outcomes.

In summary, there exists a large discrepancy between the expectations and hopes of patients participating in Phase I trials and the realistic outcomes of little therapeutic benefits and possible significant toxicity. It is certainly possible, given this, to imagine a situation in which the outcome of such uninformed participation may be detrimental to the overall wel-being and QOL of these vulnerable patients, once the anticipated therapeutic benefit fails to accrue. Therefore, the argument can be made that the psychologic wellbeing of these patients should be included in the trial outcomes, as they are vulnerable and may potentially suffer detriments to their QOL from such trial participation. Given this, it is imperative that steps be taken to recognize the need for QOL assessments in Phase I trials.

Studies measuring quality of life as an outcome in Phase I trials

TABLE 2 summarizes all studies found that satisfied the inclusion criteria for assessment of QOL as an outcome measure in Phase I trials of novel chemotherapy regimens for cancer patients (i.e., measured at least once prior to and following the intervention, as detailed in the methods section above). Indicating the novelty of assessing QOL in Phase I trials, only 12 studies were identified that met the inclusion criteria. This is among over 460 trials identified by a recent review of oncology Phase I trials conducted between 1991 and 2002 [20], and all trials published from that date until May, 2005. At best, approximately 2% of all Phase I trials included a QOL component. The number would be higher had the authors chosen to include trials of therapies other than chemotherapy (i.e., radiation therapy, vaccines or immune therapies) but not significantly so. The studies identified represent a wide range of applications and target tumor sites, including brain [5,26], pancreatic [27], colorectal [28], bladder [29] and mixed groups [25,30–35]. The majority of the studies assessing mixed groups looked at patients who may have been participating in different trials, but were grouped together for the purposes of QOL analysis.

Overall, several studies reported either no change in QOL [25,30,34] or actual improvement over the course of the trial; on wellbeing, mood, activity level [30] and pain [27], but particularly on anxiety levels [30,31,35]. This may indicate that high anxiety and anticipation before a trial is allayed over time as the trial comes to pass and no extreme adverse effects are realized. In some studies, HRQOL was lower following the trial [26,27,32,33] – this is not particularly surprising considering the populations studied – patients with incurable metastatic disease. One may expect naturally occurring decreases in functional HRQOL over time as the normal course of advanced disease progression. In one case, the treatment regimen was directly associated with decrements in QOL, as higher doses of the drug were correlated with lower QOL on the FACT [29]. Nonetheless, given the expected course of deteriorating QOL in these patients, the studies showing stable or improved QOL indicate a possible forestalling of this progression, or may be a factor of missing data and selective dropouts. Another potential benefit of measuring QOL was to engender a feeling of being cared for and understood by the healthcare team, which may subsequently increase treatment compliance and retention rates [29].

Table 2. Summary of Phase I studies with quality of life as an outcome.

Subjects	Methods	Measures	Results	Conclusions	Ref.
26 patients with multiple tumor locations. 18 (mean age = 55.5, 11 males) were undergoing Phase I protocols and eight (mean age = 54.5, four males) were undergoing standard and low efficacy cytotoxic or endocrine regimens	Nonrandomized prospective two arm pilot study. Measures were completed retrospectively to the time of diagnosis and prior to entry into the study, during the treatment and after the end of treatment	KPS was used to measure functional ability. LASA scales of a number of QOL dimensions: pain, nausea, appetite, mood and anxiety	No differences between the groups at baseline or during the period before study entry. No significant differences between the test and control groups on KPS. Both groups showed an overall positive influence of treatment on their wellbeing, mood, activity and anxiety level. Pain, nausea, appetite and social activity were not improved	No significant differences between the groups on KPS or LASA at any of the time periods. Overall, both groups improved the psychologic aspects of the LASA	[30]
55 patients with advanced cancer, mostly solid tumors (22 men and 33 women, mean age 58.8). 40% had not received any treatment prior to offer of trial	Patients were given questionnaires and interviewed (semistructured) within 48 h of consenting to the trial, after two cycles of the treatment, at the time of withdrawal or treatment completion and 6–8 weeks after trial completion	EORTC QLQ C-30 and the HADS. Interviews consisted of questions regarding recruitment experiences, information received, understanding of trial, reasons for participation, experience of trial, support needed, impact on QOL, meaning of participation and satisfaction with care received	Of initial 55 participants, 21 were dead at follow-up. No significant findings on quantitative measures. At pretrial, 54% of patients were hopeful about the trial, 58% felt uncertain and 54% felt special for being in the trial, 80% of the participants felt the trial was the best thing to do because the doctor offered it. Only 16 patients could identify the purpose of the trial	Five suggested ways that this information can be used to inform clinical trial management. These include: Acknowledge participants contributions; Prepare patient for trial participation; Enhancing continuity of palliative care; Accessing the trial participants' views; Increasing public understanding of clinical trials	[25]
55 patients (median age = 60, 22 men, 33 women) with solid lung, breast and gastrointestinal tumors	Interviews and questionnaires before participating but after consenting to trial, 6 weeks into the trial, at trial conclusion and 6–8 weeks after trial completion	Semistructured interviews, EORTC QLQ-30, HADS	Qualitative themes were: therapeutic alliance, trial burden and searching for meaning. Cognitive and emotional functioning were high and financial concerns, diarrhea, pain and sleep problems were low. Anxiety and depression were in the normal range throughout the trial but there were more patients with severe anxiety (7%) at pretrial than at posttrial (1%)	Interviews revealed that QOL was affected more than the questionnaires showed. Magnitude of questionnaire scores did not match the extent to which patients reported effect on QOL. For patients, QOL was broader than allowed to express on questionnaires	[31]
26 patients with previous radiation, CPT-11 and chronomodulated 5-FU and FA. 58% male, median age 61 (range 38–70). 81% colon, 19% rectal. 85% had metastases to the liver. 85% had a WHO performance status of 0	5-FU and FA were administered by a portable pump for 5 consecutive days every 3 weeks and CPT-11 on day 1 every 3 weeks until disease progression, intolerable toxicity or withdrawal	Response to treatment was assessed by CT scans every three courses. QOL was measured at baseline, at 9 weeks, and every 9 weeks thereafter using the EORTC QLQ-30	DLT was observed in seven patients. Neutropenia was the most common toxicity reported in 31% of patients. Diarrhea was the most serious toxicity in 26% of patients. Tumor growth control in 65% of patients. Median duration of response was 199 days and median overall survival was 359 days. QOL mean scores remained stable and were not affected by differing doses	It is possible to deliver CPT-11 with FF in pretreated colorectal cancer patients without producing more side effects or affecting QOL	[28]
23 male patients with carcinoma of the bladder, stage T2-T3. All underwent transuretheral resection, chemotherapy and radiation. Median age 62	RT administered twice daily and chemotherapy (gemcitabine) twice-weekly. Questionnaire completed before during and after therapy	FACT-G and a bladder specific version of the FACT, (FACT-BL)	No significant differences on the FACT-G or the FACT-BL between patients who received greater or less than 20 mg/m^2 were found at the three testing periods, although those who had higher doses reported lower QOL. Those who experienced DLT scored lower in QOL generally and specifically in physical wellbeing	Surgery followed by chemoradiation has a significant effect on QOL. QOL measures should be included in order to better understand patient experience. Measuring QOL may increase compliance with treatment	[29]

Table 2. Summary of Phase I studies with quality of life as an outcome.

Subjects	Methods	Measures	Results	Conclusions	Ref.
157 patients (69 in the USA, 88 in the European/Australian trial). Patients had one of five tumors (NSCLC, head and neck, colorectal, prostate or ovarian)	Patients were recruited from two open-label Phase I trials. Questionnaires were completed at baseline, days 14 and 28 of the first treatment period, on the last day of each subsequent cycle, before clinical assessment, before patients were informed of their disease status and at trial withdrawal	FACT-G was used along with the specific subscales for head and neck, colorectal, prostate and ovarian. The FACT-L was used along with its LCS. TOI component of the FACT was used to assess the more physical and functional aspects of patients QOL	In the E/A trial: QOL decreased for those patients with prostate and ovarian cancer, improved in those with NSCLC and remained the same in patients with head and neck and colorectal cancer. In the USA trial, patients with head and neck and NSCLC showed an improvement in QOL whereas those with colorectal, ovarian and prostate cancer demonstrated a worsening in their QOL	The FACT tools showed promising results for measuring QOL and were sensitive to clinical change. Patients that were on varying dosages demonstrated patterns in their QOL responses. Symptomatic improvements were observed, resulting in better QOL, especially in those with NSCLC	[32]
Nonrandomized prospective trial of 92 participants (64 in Phase I group and 28 in the supportive care group). Of those, 70 and 36% were evaluable respectively since two or more QOL evaluations were completed. The majority was male in both groups and the median ages were 60 and 62, respectively	Questionnaires were completed before treatment began and prior to each subsequent course. The time varied depending on the agent being used. For those receiving supportive care, questionnaires were administered at the time they were considered ineligible for the Phase I trial and then weekly thereafter	QOL was measured using the LASA Scale. PS was measured using the Southwest Oncology Group criteria and was determined by the physician	Overall QOL did not change for the Phase I group but decreased for the supportive group in appetite and support by doctors and nurses. The people with more than two evaluations in both groups reported a significant decrease in QOL as disease progressed and time passed. PS was significantly correlated with QOL. Phase I group had little change in PS from time one to two but the supportive group reported a considerable decrease. Median survival time for the Phase I group was 4 months compared with 1 month for the supportive group	QOL and PS are not affected by one course of Phase I trial. The supportive care group's reduction in support from doctors and nurses increases the awareness that this group may need continued support. QOL and PS information is useful for patients deciding on Phase I treatment and for those healthcare professionals recommending it	[33]
25 patients with metastatic pancreatic cancer received chemotherapy. 12 patients were female. Mean age was 62.7 years. Majority of metastases were to the liver	Patients were treated with a combination of gemcitabine and docetaxel weekly for seven different dosages of both drugs	Side effects were assessed according to WHO standards. EORTC QLQ-30 prior to beginning each chemotherapy session and after completion	Toxic effects in five patients prompted cessation of therapy. The median survival time was 12.2 months. Improvement in pain was observed in 12% of patients, quality of life in 20% and general healthcare condition in 8%. 11 patients assessed their QOL as worse than prior to therapy	The use of this regimen is tolerable, but while QOL improved in 40% of patients, it decreased in almost half	[27]
56 patients with recurrent glioblastoma (65%) or anaplastic astrocytoma (35%). All had had prior surgery, radiation and chemotherapy. Median age was 49.5 with a range of 25–67. 65% male	Patients were assessed at baseline and a follow-up prior to their next course of therapy, usually monthly until no longer in the study due to progressing disease. MRI and neurocognitive tests were always performed	Cognitive functions were assessed by the Digit Span, Digit Symbol, Hopkins Verbal Learning Test, Controlled Oral Word Association, Trial Making Test, Part A and B, and the Grooved Pegboard. QOL was assessed by the FACT-Br and ability to perform daily activities by the ADL and FIM	Patients were performing well below normal on the cognitive tasks at baseline and were not fully independent in their ADL. QOL was comparable with norms of brain tumor patients. Cognitive deterioration occurred in a median time of 7.4 weeks and was evident 50% earlier than MRI demonstrated disease progression. QOL and ADL decreases were observed well after MRI demonstrated progression. Cognitive decline occurred approximately 6 weeks before radiographic evidence. Memory and fine motor declined the most overall	QOL measurement is hard because patients had trouble understanding the questions and how to respond to them. Cognitive assessment was easier in comparison. Cognitive function can predict tumor recurrence in advance of MRI. QOL and ADL decreases were seen after tumor progression	[26]

Table 2. Summary of Phase I studies with quality of life as an outcome.

Subjects	Methods	Measures	Results	Conclusions	Ref.
747 patients with malignant glioma in a randomized dose escalation Phase I/II trial of twice-daily RT with carmusine. Age range was 19–70, most patients were male and had a prior partial resection.	Patients were randomized to four arms of hyperfractioned RT or to two accelerated hyperfractioned arms. Patients were assessed at time of randomization and at each follow-up appointment made by the physician. Number of follow-ups ranged from one to 36	Data were collected on 15 NSS as well as any grade 1–4 toxicities. QOL assessed by evaluating change from baseline on the 15 NSS, taking into consideration the severity of each symptom and the duration spent in that condition. QTIME was calculated to represent the maximum possible time (days) for each patient without appreciable neurologic symptoms. QAS considers both treatment toxicity and retreatment	The average QAS for all 747 patients was 18.5 months. The hyperfractioned arm of 72.0 Gy had significantly longer QAS with 20.8 months. Younger patients did significantly better than older patients. Patients with a low KPS did significantly worse than those with a higher KPS. Patients with a lesser grade of tumor had an average QAS of 46.7 months vs. 9.3 months. Male patients had a slightly longer QAS (17.9 months) compared with females (13.8)	QOL is especially important in those patients with high grade tumors who have a short expected survival time. Age at diagnosis, grade of tumor and KPS are all important determinants of outcome. An advantage was identified for the intermediate dose level of 72.0 Gy for all patients. Adding an objective measure of QOL may help define a cost-effective treatment	[5]
40 patients with CUPS or oesophagagastric/pancreatic adenocarcinoma. Mean age was 59 and 57.5% were male. 30 patients had CUPS, nine had oesophagagastric cancer and one had pancreatic cancer	Chemotherapy regimen of bolus intravenous 5-FU leucovorin on days 1–5 and carboplatin on day 3. The chemotherapy regimen was repeated every 4 weeks. Treatment was stopped after the sixth course unless response was shown	Toxicity was assessed using WHO guidelines. Before each chemotherapy treatment, patients were interviewed regarding their toxicity and symptomatic improvements. The EORTC QLQ-30 was completed before chemotherapy, after courses three, six, and eight as applicable	68.7% experienced a grade 3 or 4 toxicity and 19 patients required dose reductions. One toxic death occurred. Symptomatic response was demonstrated by an improvement in 50% of patients with dysphagia, 79% of patients with reflux, 71% of patients with pain and 80% of patients with nausea. 86% of the patients gained weight. No significant improvement or deterioration in QOL could be shown	This chemotherapy regimen showed comparable results to other platinum based regimens in patients with CUPS, good symptomatic improvement and no deterioration in QOL	[34]
10 patients (six women) involved in Phase I trials. eight were on a combination of fluorouracil, folinic acid and interferon and the other two were taking proprietary experimental drugs. Age ranged from 45–71 and a variety of cancers were represented.	Daily diary kept and the MAC, HADS and RCSL completed before the trial. After the trial, the HADS and RSCL were repeated. Patients were interviewed over the next 4 weeks to assess their experience and motivations for participation	Adjustment was measured with the MAC scale. Mental health was assessed using the HADS and QOL with the RSCL. The daily diary was comprised of three parts: 13-item chemotherapy and disease related symptom checklist; A mood assessment including two questions from each of the POMS subscales; and psychologic coping was based on eight items from the COPE scale	Seeking social support for instrumental and emotional reasons fluctuated over the course of the trial, being more common during times of hospitalization Psychologic wellbeing did not significantly fluctuate over the course of the trial. The mean score of the HADS anxiety subscale improved but not the depression scale. There were no significant results on the physical symptom subscales	Coping responses change over time while in a Phase I trial, particularly after being hospitalized. There were significant differences in individual coping styles. This sample was not highly distressed and was comparable to other published reports. QOL may be improved by the intense contact with staff during the trial and these results support the notion that there may be psychologic benefits to participation	[35]

ADL: Activities of daily living; CPT: 11-Irinotecan; CT: Computed tomography; CUPS: Carcinoma of unknown primary; DLT: Dose limiting toxicity; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; 5-FU: 5-fluorouracil; FA: Folinic acid, FACT-Functional Assessment of Cancer Treatment; FIM: Functional Independence Measure; HADS: Hospital Anxiety and Depression Scale; KPS: Karnofsky Performance Scale; LASA: Linear analog self-assessment; LCS: Lung Cancer Subscale; MAC: Mental adjustment to cancer; MRI: Magnetic resonance imaging; NSCLC: Nonsmall cell lung cancer; NSS: Neurologic signs and symptoms; POMS: Profile of Mood States; PS: Performance status; QAS: Quality-adjusted survival; QOL: Quality of life; QTIME: Quality survival time; RCSL: Rotterdam Symptom Checklist, RT: Radiation Therapy; SEIQOL-DW: Schedule for the evaluation of individual quality of life-direct weighting; TOI: Trial outcomes index; WHO: World Health Organization.

Interestingly, in one study, trial participation resulted in increased QOL on the FACT in patients with lung cancer, but decreased QOL in patients with prostate and ovarian cancer, whereas in patients with head and neck and colorectal cancer there was no change [32]. This may point to the importance of considering baseline QOL prior to trial participation in different groups. Typically, QOL for patients with lung cancer is amongst the lowest, so trial participation may lead to QOL improvements as new drugs may forestall some of the disease progression causing symptomatology, whereas for patients with prostate and ovarian cancer who may not be as symptomatic at the outset, introducing more toxicity may lead to decreased QOL levels.

Other research has highlighted the importance of qualitative data in fully understanding QOL issues in trial participants. Although standard questionnaires revealed either no changes or small decreases in anxiety, clinical interviews showed more QOL effects than questionnaires reported; the magnitude of the questionnaire scores did not match what the patients said about effects on QOL. For the patients, QOL was determined more broadly than what the questionnaires (the EORTC and HADS) measured [31]. This is a common criticism of HRQOL measures: they focus primarily on domains of QOL that are directly related to physical health, such as functional status, but often disregard other aspects of import in people's lives, such as spirituality, family relationships and positive growth.

Indeed other studies have found that patients nominate health and family as equally important using the SEIQOL [9,10]. However, a recent study found the most commonly spontaneously nominated areas of QOL for patients in a Phase I trial were family relationships, activities and friends, with surprisingly few mentions of health status [14]. This type of study highlights the importance of not overlooking the subjective and individualized evaluation of patients themselves, where areas that determine QOL may not always correspond to those measured by most HRQOL measures summarized in TABLE 1.

Other researchers have used QAS as an outcome – one of the measures that combines both length of survival with QOL during that time. Using this technique, researchers were able to demonstrate that a particular treatment regimen provided longer QAS than others [5]. This type of analysis is important as it takes into account not just increased duration of survival due to a particular treatment, but also how a patient feels during that time. For patients who often value QOL as highly as quantity this may be a much more meaningful way to report primary outcomes of these types of trials [11].

Issues regarding quality-of- life measurement in Phase I trials

Despite obvious advantages to both patients and practitioners, the measurement of QOL in patients with advanced cancer is vulnerable to some serious methodologic concerns. Of utmost relevance is the prevalence of missing data. Given the fact that patients enrolled in these trials have advanced cancers, the percentage of data lost due to death and deteriorating health is a valid concern. For example, in a Phase II/III study that examined QOL, the percentage of data lost for this reason was 46% [36]. This makes it difficult to determine the longitudinal effect of the trial on the QOL of the sample due to reductions in sample size. A further problem with this area of research is the bias that results from using only the QOL data from patients who are well enough to complete the questionnaires and survive long enough to complete all assessments [36]. This may be one explanation for the absence of QOL change reported in some of the studies this authors reviewed. A study by the Meta-analysis Group in Cancer [37] found that the patients who remained in the trial had relatively stable QOL compared with the QOL of those who withdrew due to deterioration or death. Additionally, the relatively small sample sizes involved in Phase I trials and the lack of comparison groups makes the interpretation of QOL results difficult [24]. Although this limitation may affect the ability to make definitive conclusions, the results obtained can provide an idea of the QOL areas potentially affected, and Phase II/III studies can be designed with these in mind [38]. Sophisticated statistic techniques for determining if data are missing at random or systematically, and imputing missing data, are available in these situations [2].

Trends in recent years have been moving towards evidenced-based medicine and clinical practice guidelines, guided by the outcomes movement of the early 1990s. More recently, emphasis has been placed on the use of PROs in determining the evidence upon which clinical decisions are based, and guidelines developed for choosing appropriate PRO measures [1,39]. The authors' argument that QOL outcomes should be factored into determining the toxicity of treatments is consistent with this patient-focused trend. The choice of appropriate QOL measures should be guided by the conceptual question a researcher wishes to address. For measuring what we have called toxicity, measures that focus on functional and practical abilities likely to be directly affected by the treatment might be most relevant. Norms and cutoff scores for what would be considered grades of toxicity on QOL measures of this nature have yet to be delineated. However, for measures of distress, reliable cutoffs have been determined. It could be stated in a trial protocol that any escalation of distress beyond clinical cutoffs be considered toxic to patients. The Brief Symptom Inventory, Beck Depression Inventory, Center for Epidemiological Studies-Depression Scale and HADS all have well-established clinical cutoff criteria that could be utilized in this manner. Whether escalation in distress would be directly due to toxicity of the drugs given, or the effect of the stress of participating in a trial itself, could be clarified using qualitative methods.

If the question is one of considering the trade-off of QOL for quantity of life, composite measures such as QAS take into account not only how long a person survives following a treatment, but what the quality of that time is likely to be. The advantage of this approach tends to be on a societal level, when making policy decisions regarding standard treatments and clinical guidelines. The disadvantage of QAS-type measures, however, is that a universally determined QOL value is usually applied to all people having

undergone the procedure in question. While this may be accurate on an aggregate level, it does not necessarily apply to each individual. Indeed, individuals vary considerably in their own self-rated QOL following identical treatments.

With the limitations and methodologic concerns of quantitative measures of QOL in mind, some researchers have moved towards using qualitative measures or a combination of research methods to understand the experience of patients participating in Phase I clinical trials. This may be advantageous if the intention of the study is to understand the whole experience of the patient, considering that some quantitative measures focus more on physical and functional QOL and less on psychologic QOL [38]. Qualitative methods might also help to distinguish between the direct effects of an investigational agent on QOL, and the positive or negative effects of simply participating in a Phase I trial. It would seem important to attempt to disentangle the effects of participation itself on hopes and expectations from the toxic or beneficial effects of the treatments directly on QOL. Some combination of standardized HRQOL measures and subjective reports of patient experience may help with this process of disentangling.

Summary & conclusions

Phase I clinical trials serve as the initial introduction of a novel therapeutic in human beings and play an important role in the development of effective treatments for cancer and many other serious illnesses. Although patients identify QOL to be as important as quantity of life, QOL is not routinely assessed in these trials. Adding QOL assessments in Phase I trials results in several benefits to patients and researchers, despite difficulties such as collecting full longitudinal data and choosing appropriate measures. Patients may feel more cared for as a whole person when their wellbeing is monitored, and this type of assessment may enhance retention rates in Phase I trials, as suggested by Herman [29].

Researchers benefit from QOL assessments as a method to translate clinical changes into patient-centered outcomes [1]. This is particularly significant in Phase I trials where disease response is not an endpoint and the preservation of QOL may be of utmost importance to the patient. In addition, patients may be able to influence the delivery of clinical trials by translating their experience into meaningful recommendations for the future. This is demonstrated in the results reported by Cox where an analysis of interviews revealed five suggestions to inform and improve clinical trial management [25]. Lastly, patients may be more capable to choose whether to participate in clinical trials if they are made aware of the effect that the trial may have on their QOL. The informed patient can make the choice between the impact of adverse events or toxicity versus potentially small gains in survival.

Unfortunately, our knowledge about QOL effects on Phase I trials is very limited due to the paucity of studies including such measures; however, those that have monitored QOL revealed interesting findings. Results were quite mixed, with studies showing improved QOL, particularly decreased anxiety levels, while others documented decreases in HRQOL or no changes. Part of these discrepancies may be due to the baseline QOL of patients entering the trial, the toxicity profiles of the specific agents being tested and the QOL outcome measures used. The usual HRQOL measures may be lacking a broad enough assessment of patients' concerns and factors that affect their QOL. Therefore, qualitative methods (e.g., interviews and focus groups) or the use of questionnaires such as the SEIQOL-DW, which measures the patients own nominated list of important life domains, may better reflect the important areas of QOL for individual patients.

Expert commentary

Phase I trials in oncology are primarily used to determine toxicity and dosing. Researchers have an ethical obligation to assure that these trials do not harm participants, including harm to QOL. Therefore, within the bounds of methodologic limitations, QOL assessments may currently be an important endpoint to consider and especially so in the future. Given the importance of QOL to patients in decision-making about undergoing new treatments, and the potential and observed impact of Phase I trial participation on QOL, it seems important that QOL should be considered when evaluating any novel intervention and be integrated into the concept of measuring the toxicity of the treatment. For this purpose, specific criteria defining QOL toxicity need to be developed. In addition to investigating the direct impact of the treatment on QOL, the psychologic effects of being part of such a trial need to be further explored in this vulnerable group of patients. Researchers may also want to consider measuring QOL in novel ways in these smaller trials, where qualitative methods such as interviews would be more manageable.

Methodologic and conceptual issues around QOL assessment such as choice of measurements, missing data and interpretation need to be taken into account when designing trials, but do not negate the usefulness of the data gathered, as indicated by review of the few studies that have thus far included QOL assessment. Interesting results regarding effects of treatment on HRQOL in different groups of patients, and the trade-off between QOL and quantity of life associated with different treatments were found that will be useful for clinical decision-making. The data provided from papers that assessed patients attitudes, beliefs and misconceptions about trial participation documented the large gulf between what really happens in Phase I trials (i.e., very little direct benefit to trial participants), and what patients believe to be the potential outcomes (a good chance of personal benefit). This highlights the possible ethical conflicts in conducting this type of research, and the vulnerability of these patients. Therefore, using QOL assessment to verify that trial participation is not directly harmful to patients is an ethically sound consideration. It may be argued that researchers, in fact, have a moral obligation to assure that patients are not psychologically or spiritually harmed by such participation.

Five-year view

Phase I research has moved increasingly into the evaluation of different types of treatments beyond chemotherapy drugs and radiation, and will continue this trajectory over the next 5 years. Immune therapy, targeted gene therapy, anti-angiogenic factors and combinations of modalities of treatments are becoming the norm. In fact, a review of studies from 1991–2002 found that more than two-thirds (71%) were using multiagent and multimodal treatments [18]. Therefore, the model of assessing toxicity as the primary outcome may require some modification, as traditional markers of toxicity caused by chemotherapy drugs may not be appropriate measures. For example, there may be no limit to the dose of a targeted vaccine or gene therapy that an individual can tolerate, therefore, other endpoints are being developed with these considerations in mind. In that context, QOL may become an important marker of a treatment's tolerability, as the extreme markers of traditional toxicity may be absent. Norms and cutoffs for QOL toxicity will need to be developed in order to apply these considerations consistently.

In addition to these considerations, outcomes combining economic analysis with measures of QAS will become increasingly common in settings focused on the bottom line. Therefore, further sophistication and training in methods of economic analysis of costs and benefits of new interventions, including integration of the crucial QOL component, will become increasingly important.

Finally, conceptual and measurement issues around what constitutes QOL, and how best to assess it, will continue to evolve. Combining both qualitative (e.g., interviews, focus groups, observation or personally-selected QOL domains) and quantitative (i.e., standard validated questionnaires) methods will become increasingly popular [40]. The definition of what constitutes QOL will also continue to evolve, perhaps incorporating not only the standard HRQOL model of focusing on health-related items, but also including broader assessment of the totality of the human experience of cancer, which affects not only daily functioning and symptoms, but also ones life priorities, values, beliefs and sense of spirituality, interconnection with others and personal growth. Whether these are appropriate domains to consider in the context of testing new treatments for advanced cancer is in itself a valid research question.

Hence, the field of advancing our knowledge of what it is like for patients with incurable cancer to participate in the development of novel therapeutics is still in its infancy. Questions remain about patient motivations, the nature of altruism versus expectation of personal gain, informed consent and the ethics of this type of research, in addition to toxicity questions of specific agents. For the field to continue moving forward, researchers may need to seriously consider these important issues, and adopt QOL testing as a central part of the model of Phase I development.

Acknowledgements

Linda Carlson is supported by a Canadian Institutes of Health Research New Investigator Award. Sheila Garland is supported by a Canadian Institutes of Health Research operating grant awarded to J Steven A Simpson and Linda E Carlson, and a Sociobehavioural Cancer Research Network Satellite Centre Grant (from the National Cancer Institute of Canada) awarded to Barry Bultz and Linda E Carlson.

Key issues

- Quality of life (QOL) is a specific term encompassing a broad spectrum of issues, including physical, social, cognitive, spiritual, emotional and role functioning as well as psychologic symptomatology and pain.
- Many measures and techniques exist for assessing QOL with considerable variation in what they measure, hence they are often not directly comparable with one another – researchers need to consider their own specific objectives when choosing measures (i.e., what would be most useful to know and for what reason?).
- Phase I cancer chemotherapy trials are designed as the first test of new drug compounds, typically in advanced stage patients with no other treatment options.
- Only approximately 5% of patients on Phase I trials will experience a tumor response from the treatment, but as many as 85% participate with hopes of personal benefit.
- Patients participating in Phase I trials feel that QOL is just as important as length of life.
- Due to the high expectations and vulnerability of patients going into Phase I trials, and the importance they place on QOL outcomes, these should be routinely measured in Phase I studies.
- Some studies that have measured QOL in Phase I trials have found few detrimental outcomes of the novel therapeutics, and some potential improvements, particularly on anxiety levels.
- Other studies found decreases in QOL over the course of Phase I trials.
- Problems with QOL measurement in Phase I trials such as missing data, drop-out of more ill patients, noncomparability of measures and choosing appropriate measures need to be considered in study designs.
- Despite these difficulties, future studies should include QOL measurement in Phase I trials as both an ethical and clinical imperative, respecting the importance of patient reported outcomes.

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