Quality of life as a primary end point in oncology

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Summary

Background: In cancer clinical trials, the standard end points include response rates, progression free and overall survival, toxicity. These evaluation criteria do not measure how the cancer and its treatment affect the quality of life of cancer patients.

Design: The relevant literature was reviewed for the purposes of determining when, how and why quality of life should be measured in cancer clinical trials. The resulting clinical benefits were also reviewed.

Results: Along with survival, quality of life is the main end point of comparative clinical trials. Its evaluation can provide physicians and patients with important information and help to identify a better treatment. Cancer-specific questionnaires with forms for specific tumour types sites have been developed and have proven to be more sensitive to changes than generic questionnaires. Quality-of-life evaluation before the start of treatment may be an important prognostic factor, even independent from performance status. Clinical benefit assessment presents important shortcomings and the clinical relevance of this evaluation should be interpreted with caution.

Conclusions: Quality of life is a fundamental task of oncological research. More studies are necessary to overcome the difficulties in assessing and interpreting this concept and the clinical benefits based on it.

Key words: clinical benefit, quality of life, research end point.

Introduction

A committee of the American Society of Clinical Oncology published the criteria to evaluate the outcomes of cancer treatment [1]. This treatment should be concerned with two types of effects: cancer outcomes, such as complete and partial response, response duration, time to disease progression, which can be regarded as activity indices, and patient outcomes, essentially survival and quality of life, which can be considered as indices of efficacy. The distinction between the activity and efficacy of antineoplastic agents is very important; phase II studies are planned to demonstrate the activity of the drug, while phase III studies have as a main objective the evaluation of the efficacy. In clinical trials, the utility of quantifying cancer outcomes is based on their potential to predict patient outcomes. Unfortunately, it is clear that an active drug is not necessarily an efficacious drug; in fact, the shrinkage or the disappearance of the tumoral mass are only premises that are necessary but not sufficient to obtain an increase in the survival or an improvement in the quality of life of cancer patients, the real tests of clinical efficacy.

A new treatment shown to be able to improve the overall survival obtained by a previously available 'gold standard' should be considered the most effective therapy and, therefore, the treatment of choice. More often, unfortunately, the main purpose of cancer treatment is not to cure, but rather to control symptoms and/or delay the disease's progression. In these cases, the improvement of patient’s quality of life is the primary goal of treatment.

What is quality of life in oncology?

In 1948, the World Health Organization defined health as not only the absence of disease and infirmity but also as the presence of physical, mental and social well-being. Therefore, health-related quality of life is a concept referring to the effect of an illness and its therapy upon a patient’s physical, psychological and social well-being as perceived by the patient himself.

Of course, quality of life is influenced by many factors other than those related to health, including economic security, freedom, job satisfaction, state of the environment, etc.; these aspects often have nothing to do with health or medicine. Therefore, clinicians when focusing on health-related quality of life should consider that, for extremely sick patients, almost any aspect of life can be regarded as health related [2].

Four factors contribute the most to the overall impact of the disease and its treatment on a patient's quality of life: physical and occupational function (strength, energy, ability to carry on expected normal activities), psychological state (depression, anxiety, fear, well-being), social interaction (with family members, with friends) and somatic sensations (symptoms due to the disease or treatment toxicity).
When to measure quality of life in oncology?

Quality of life in oncology has been evaluated in descriptive phase II and phase III studies. It is very important to acknowledge the limitations of such quality-of-life evaluation in each of these types of studies in order to better understand and interpret their results.

Descriptive studies are useful to obtain information about the impact of a treatment on the quality of life (i.e., to show the persistent or recurrent distress in patients with small-cell lung cancer who are long survivors after a cytotoxic treatment). The results of descriptive studies might indicate specific interventions to ameliorate quality of life. With descriptive studies, patients can be informed about the risks and benefits of the treatments before their administration. Unfortunately, being non-comparative, descriptive studies do not permit patients so informed to choose among different alternative treatment options. Furthermore, as only a minority of the population is enrolled in such studies, a selection bias should be considered in the interpretation of the results. Therefore, descriptive studies are useful only as generators of hypotheses, which are to be verified subsequently in prospective controlled clinical trials.

The usefulness of evaluating concerns about the quality of life in clinical phase II studies is still debated: such studies evaluate drug activity but cannot establish what is its contribution to quality of life. Such studies do not allow us to distinguish between the negative impact of treatment toxicity and the positive impact of symptom control. However, the evaluation of the activity of palliative treatments, along with an observed improvement of some factors governing the quality of life, especially if the treatment is well tolerated, can suggest a potential efficacy of the drug.

Evaluating the quality of life in phase III studies is very important, as it can lead to definitive conclusions about the efficacy of one of the treatments. Resources may not permit the assessment of the quality of life in every randomized clinical trial. It is, however, a priority to measure it in phase III studies when two conditions are satisfied: 1) the predicted survival differences among the treatment arms are expected to be small (a very frequent scenario) and 2) the predicted differences in at least one of the factors governing the quality of life are expected to be quite large.

How to measure quality of life in oncology?

In clinical trials the most common approach to the evaluations of the quality of life is through self-administered questionnaires, although other techniques (i.e., personal or telephone interviews) may also be used, as described in another contribution to this journal supplement.

The necessary attributes of any instrument for measuring the quality of life include:

- **reproducibility**: its ability to yield the same results on repeated trials under the same conditions;
- **validity**: the accuracy with which it measures what it is supposed to measure;
- **responsiveness**: the ability to detect clinically significant changes over time;
- **interpretability**: the ability to provide results which can make sense.

In particular, clinicians should understand the significance of any observed difference between groups of patients or between treatments.

The measurement of the health-related factors governing the quality of life is characterized by two basic approaches involving generic and specific instruments. Generic instruments can be further divided in two major classes: health profiles and utility measurements.

Health profiles are single instruments that attempt to measure each important aspect of the quality of life. Being generic measures, they are designed to be used in a wide variety of conditions. Health profiles offer a number of advantages to clinical investigators: their reproducibility and validity has been well established, and they can depict the different effects of treatment in different medical conditions and among different studies.

On the other hand, health profiles do have some limitations: it is possible that they do not focus adequately on some specific aspects of the quality of life and are not responsive enough (possibly failing to detect small but still clinically important changes in quality of life). They often suffer from other limitations, such as being lengthy and time-consuming for the patient to complete. Among the health profile questionnaires, the SIP (Sickness Impact Profile, that includes 136 items), the NHP (Nottingham Health Profile, 38 items) and the SF-36 (Short Form-36 Health Survey, 36 items) are the most widely utilized.

Utility measurements indicate the individual preference for a specific health status. With utility measurements the quality of life is summarized as a single number along a continuum that is usually extended from death (0) to full health (1). The preference expressed by utility measurements may come directly from individual patients, from physicians or from the general population asked to rate the value of different states of health presented in the form of scenarios. The most commonly used methods are the rating scale, visual analogue scale, the standard gamble and the time trade-off approach.

Utility measurements can be used in cost–utility analyses that consider duration and quality of life in combination. Utility measurements also have limitations. In fact, utility scores can vary depending on the method used to obtain them (those which are obtained from patients are generally higher than those provided by physicians, which are, in turn, higher than utilities for the same health states obtained from healthy individuals) and on the kind of approach used (the few studies that have been conducted to compare simultaneous measurements of utilities using different approaches have found
these approaches to be, at best, only moderately correlated. Utility results do not allow the investigator to determine the aspects of the quality of life that are responsible for utility changes. Finally, utility measurements may not be responsive to small but still important clinical changes.

Specific instruments focus on the aspects of health that are specific to the area of primary interest. The rationale for this approach lies in the potential for increased responsiveness that may result from the inclusion of only those elements concerning the quality of life that are relevant to the specific patient population. The instruments may also be disease-specific (i.e., cancer); in this case, they have a core number of quality-of-life factors that are constant for each patient.

Among these specific instruments are the FLIC (Functional Living Index-Cancer, 22 items), the EORTC (European Organization of Research on Treatment of Cancer, 30 items), the CARES (Cancer Rehabilitation Evaluation System, 59 items) and the FACT (Functional Assessment of Cancer Therapy, 27 items). Other instruments are organ- or treatment-specific; among these are the modules used with the EORTC and FACT questionnaires (lung, breast, bladder, prostate, etc.).

The disadvantages of specific measurements are that they are deliberately not comprehensive and cannot be used to make comparisons across different conditions.

In conclusion, in clinical trials specific questionnaires should be preferred because they are more responsive in detecting small treatment-induced changes, while generic measurements may be particularly useful for surveys that attempt to document the range of disability in a general population or patient group.

**Why measure quality of life in oncology?**

1. First, standard end points do not measure the effects of cancer or its treatment on the emotional, spiritual and social dimensions of patients' lives. The description of how two compared treatments influence quality of life and overall survival is important to select the best treatment [3]. In fact:
   - a treatment may be preferred if it improves the quality of life even if the survival is not superior to that conferred by the comparable treatment;
   - a treatment may be unsatisfactory and should not be used in clinical practice when quality of life worsens or remains similar to that under the comparable treatment without advantages in terms of survival.

However, there are two situations in which the outcome is difficult to interpret:
   - if the treatment induces a lower chance of survival but quality of life improves;
   - if quality of life is worse but chances of survival are improved by the treatment. Of course, if the survival improvement is large and the duration of the poor quality of life is short, the choice may not be too difficult.

In these two situations, one may make a choice by
- either describing to patients in a detailed scenario the positive and negative effects on quality of life and survival for each treatment in order to achieve a choice jointly made by the patients and the physician [4]
- or by resorting to measures that combine quality with quantity of life such as QALY (Quality-Adjusted Life Years) and Q-TWIST (Quality-adjusted Time Without Symptoms and Toxicity).

Both these measures are obtained multiplying the duration of survival (treatment efficacy) by the utility score (quality of life perceived by the patient).

2. Evaluating the quality of life can be important for the cost–utility analysis of new drugs or combinations [5]. The choice among different treatment options has also to consider their cost, as it is extremely important to control the health expenditure from appropriately allocated scarce resources.

3. Quality-of-life studies are not simple extensions of toxicity scales. These scales measure only the maximum toxicity observed in a patient but do not take into account the duration of toxicity, while quality-of-life instruments do take this point into account. Furthermore, there is less effect on quality of life from acute than from chronic and late toxicity. For example, patients with debilitating neuropathy often have a very poor quality of life, despite good control of their cancer.

4. The physician frequently is quite intuitive when determining what can be done for the patient in order to maximize the patient's quality of life. Sometimes, however, counter-intuitive results are observed. For example, an aggressive therapy may result in an improved quality of life. Coates compared continuous versus intermittent chemotherapy in patients with metastatic breast cancer [6]. Unexpectedly, patients on continuous chemotherapy had a better quality of life and also survived longer, but these data are actually subject to criticism (see the paper by Mosconi in this supplement).

5. Quality-of-life instruments may provide prognostic information independent of other factors (including performance status) in the patient population studied. This has been shown in patients with breast, lung, gastrointestinal cancer and melanoma [7]. If these results are confirmed, initial quality of life should be measured in all patients and used as a stratification factor in randomized clinical trials.

**Clinical benefit**

Considering that for most disseminated cancers, the main objective of the treatment is symptom control and the difficulties in assessing and interpreting quality of life results (see the paper by Ballatori in this supplement), the concept of 'clinical benefit' has been developed as a new patient outcome.
Clinical benefit addresses the beneficial effects of a treatment in improving disease-related symptoms more than its ability to induce a cancer outcome (partial or complete response, etc.). On the basis of this end point, the Food and Drug Administration approved gemcitabine for patients with pancreatic carcinoma refractory to fluorouracil and mitoxantrone for hormone-refractory prostate carcinoma.

In the two gemcitabine studies, clinical benefit expresses a composite assessment of the treatment's effect on pain (measured according to its intensity and to analgesic consumption), Karnofsky Performance Status and changes of body weight [8, 9]. Gemcitabine was shown to induce a clinical benefit in over 20% of patients, a rate statistically significantly superior to the clinical benefit obtained with fluorouracil. Furthermore, gemcitabine increased significantly the median survival (5.65 vs. 3.85 months) and induced more hematological toxicity (grade 3 and 4 granulocytopenia in 25.9% vs. 4.9% of patients).

In the mitoxantrone study, the clinical benefit consisted in a two-point reduction of pain out of a six-point descriptive scale that was achieved by 29% of patients receiving mitoxantrone plus prednisone, compared to 12% of patients receiving prednisone alone [10].

Clinical benefit as an outcome has important shortcomings [11]:

1. Any clinical benefit must be always weighed against the treatment's toxicity. Chemotherapy induces adverse events that, even when mild, might have a negative impact on a patient's quality of life. For example, patients treated with gemcitabine have usually more grade 3–4 neutropenia and fever episodes than those receiving fluorouracil [9]. Therefore, to correctly evaluate the chemotherapy impact, it should be important to adjust the clinical benefit to the adverse events, but this has not so far been done.

2. Due to the subjectivity in evaluating the responses, a double-blind trial should be carried out, but this is impossible when chemotherapy treatment is in only one of the study arms.

3. The clinical relevance of clinical benefit should be interpreted with caution. In fact, clinical benefit has not been validated, nor is a comparison available with validated instruments by which to measure the quality of life.

4. Considering the high cost of gemcitabine and mitoxantrone, a cost–utility study should be made to evaluate the cost per unit benefit obtained from the patient's point of view.

References


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