Health and Quality of Life Outcomes

Commentary

Surrogate end points of quality of life assessment: have we really found what we are looking for?

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Abstract

Outcome research is a new interesting field in medical research. Some years ago, a document of the American Society of Clinical Oncology distinguished the outcomes of a treatment into *patient-outcomes* (overall survival and quality of life) and *cancer-outcomes* (response rate), giving higher priority to patient outcomes. This document is one of the best structured instruments to evaluate and classify the outcomes in clinical oncology. Nevertheless, although overall survival and quality of life represent the main patient outcomes in clinical oncology, in the last years many researchers tried to overcome these recommendations, creating new surrogate end points to assess overall survival and quality of life. Surrogate end points can be useful tools when they are used to achieve preliminary data that anticipate the evaluation of the final outcome, but the use of surrogate end points *instead of* the main outcomes is quite dangerous, as it can provide wrong answers to clinical questions. The use (or abuse) of surrogate end points of quality of life has recently favoured some questionable decisions of the main regulator organs, such as the approval by the Food and Drugs Administration of the use of gemcitabine in advanced chemotherapy-naive pancreatic cancer, or mitoxantrone in the palliative treatment of hormone-resistant pancreatic cancer, based on the improvement in *clinical benefit* (a non-validated instrument to evaluate the outcome of palliative chemotherapy) besides a minimal and questionable overall survival, or *pain control* (evaluated with a non-validated instrument). A correct use of surrogate end points of quality of life *within* and not *instead of* quality of life assessment should be the engagement of our further efforts in quality of life research.

Introduction

In the last years, many authors highlighted the importance of outcome research in oncology, either in clinical research or in daily clinical practice [1,2]. Outcome research has been defined as a discipline investigating the relationship between the results of clinical research and clinical practice, but a consensus about the real meaning of outcome is not yet fully reached, and many aspects are not well defined. In 1996, the American Society of Clinical Oncology (ASCO) published a special article to clarify the outcomes of a clinical approach to neoplastic disease [3]. Based on the distinction between *activity* and *effectiveness* of a treatment, the outcomes were divided into *cancer-outcomes* (response rate) and *patient-outcomes* (mainly survival and quality of life). Moreover, the Outcomes Working Group of the ASCO highlighted the priority of patient-outcomes, giving a secondary relevance to cancer outcomes and pharmacoeconomic evaluations. The relevance of survival and quality of life as patient-outcomes entails two critical issues: a) how to correlate the different

outcomes in the same clinical approach; and b) how to evaluate the outcomes in daily clinical practice or clinical research from a methodological point of view.

In daily clinical practice, response rate is the main criterion to evaluate the outcome of a treatment, as a relationship between response rate and overall survival is supposed. However, such an assumption can be acceptable for chemo-sensitive diseases (Hodgkin disease, testicular cancer), but it is at least questionable for the most part of chemo-resistant diseases (Non-Small-Cell Lung Cancer, gastric or pancreatic cancer). A similar questionable attitude is represented by the increasing use of symptoms control, toxicity or performance status as surrogate end points of quality of life, whereas the actual assessment of quality of life remains a neglected end point in clinical research. Despite the dangerous implications from a methodological point of view, the use of surrogate end points of effectiveness is a quite diffuse attitude, that is rapidly increasing in both clinical research and daily clinical practice. Although the Food and Drugs Administration (FDA) and EMEA give great relevance to quality of life as a patient-outcome [1,4], they do not seem to consider quality of life as an essential outcome when they are approving new drugs [5,6]. Such an idiosyncrasy of both clinicians and regulatory agencies for the assessment of quality of life has favoured the use of several surrogate end points, potentially misleading and methodologically questionable.

Surrogate end points of quality of life

In the last years, clinical research paid increasing attention to quality of life, and many papers investigated quality of life as an outcome of the treatment and improvement in the quality of the data [7-9]. However, the assessment of quality of life is difficult and often inaccurate. Frequent obstacles in quality of life assessment are represented by patients compliance, missing data, accuracy of the assessment, usefulness of the tools (validated and not-validated), complexity of the assessment, and scepticism of clinicians, researchers and regulators about the value of health-related quality of life assessment in clinical research or in clinical practice [10-16]. All these obstacles have favoured the use (and the abuse) of surrogate end points of quality of life, the role of which has invaded the main dimensions of quality of life research, jeopardizing the correct assessment of health-related quality of life as a patient-outcome. Surrogate end points are intermediate end points, that should be related with the main end point and could represent a preliminary index of the final outcome. Surrogate end points of survival can be the disease free interval in the adjuvant setting, or the number of complete regressions of the disease during chemotherapy for metastatic cancer [3]. Both parameters, although different from overall survival, may represent a preliminary index of effectiveness, that can be useful in a preliminary analysis. Although a preliminary evaluation of effectiveness with a surrogate end point can be extremely useful if related with the final outcome, it could be deleterious if used *instead of* the evaluation of the final outcome. The risk of confounding a surrogate end point with a final end point is a real danger for researchers and regulators, and the misunderstanding between surrogate and final end points is not uncommon in oncology.

Surrogate end points of quality of life assessment: reasons for the recent misunderstanding

In the last years, the "clinical benefit assessment" has widely been used to evaluate the outcome of palliative chemotherapy [17]. It was introduced in 1996 by Rothemberg et al. as a primary end point in a phase II trial investigating the activity of gemcitabine in metastatic pancreatic cancer pre-treated with 5FU [18], and consisted of the measurement of three debilitating signs or symptoms, frequent in advanced pancreatic cancer: pain, functional impairment and weight loss. The trial showed an activity of this palliative treatment, and was followed by a phase III trial, that reported an improvement in clinical benefit and survival for patients with chemotherapy-naive pancreatic cancer treated with gemcitabine, in comparison with patients treated with 5FU [19]. Both these trials, introducing clinical benefit as an outcome of palliative chemotherapy, were severely questioned [20-24] for the following methodological reasons:

- Clinical benefit has never been validated as an outcome of a palliative treatment in pancreatic cancer.

- Although clinical benefit assessment derived from the assessment of two primary measures (pain and performance status) and one secondary measure (weight change), it was just pain (in particular the reduction in opiate consumption) that significantly differed between responders and non-responders; this could not be considered enough to justify an approach with chemotherapy.

- The effectiveness of gemcitabine as palliative treatment had to be tested against an appropriate palliative treatment (in particular, considering the relevance of pain assessment in clinical benefit evaluation, against an adequate treatment with opiate), avoiding to use the reduction of opiate consumption as a partial index of activity.

- The weight of costs and side effects was not adequately compared with the modest and questionable improvement in the primary end points.

However, these severe criticisms, raised by many authors, failed to restrict the use of clinical benefit as a surrogate

end point of quality of life. On the contrary, it has become one of the main outcomes not only in the palliative treatment of advanced pancreatic cancer, but also of many other solid tumours [25,26]. Moreover, on the basis of the improvement in overall survival and clinical benefit [19], in 1997 the FDA registered gemcitabine as the treatment of choice in advanced pancreatic cancer, assuming clinical benefit as a surrogate end point of quality of life, and paving the way for a new dangerous era in quality of life assessment.

Likewise, in 1996 Tannock et al. published the results of a trial investigating the use of mitoxantrone in advanced hormone-resistant prostate cancer [27]. Also this trial had some limits, that were similar to those weakening the trials focused on clinical benefit in advanced pancreatic cancer: primary end point was pain control; pain was assessed using non-validated instruments; the reduction in opiate consumption was a secondary end point; the control arm received corticosteroids, that is a questionable treatment if pain control is the primary end point. Nevertheless, mitoxantrone was registered by the FDA for the treatment of advanced hormone-resistant prostate cancer, adopting pain control (assessed with a non-validated instrument) as a surrogate end point of quality of life, despite the criticisms and the doubts widely expressed in literature [28-30]. The group of Tannock successively reviewed the data of their first experience, analysing either the quality of life [31], or the pharmacoeconomic dimension, correctly using a cost-utility model of analysis [32]. Both reports confirmed the superiority of the experimental arm, but some perplexities do remain, for either the choice of the control arm (low doses of prednisone are not universally accepted as the standard palliative treatment in hormone-resistant prostate cancer), or the rapid approval by regulators on the basis of the data of the first paper. Also for the use of mitoxantrone in hormone-resistant prostate cancer it is evident how dangerous could be an approach to quality of life based on surrogate end points.

A different, but in one way similar question may be represented by the recent FDA rapid approval of gefitinib in the treatment of advanced pre-treated Non-Small-Cell Lung Cancer. Although in the IDEAL-1 and the IDEAL-2 trials (the registrative trials) were used validated tools in quality of life assessment, both of them were planned as phase II trials, in which the activity, and not the effectiveness of the treatment were investigated [33-36]. It follows that a correct tool on one hand, but also an inappropriate design of the trial on the other hand, were used to register a molecule in the treatment of cancer, underlining once again how the topic may be still confounding (although the rules of FDA rapid approval of a drug are obviously beyond the arguments of this paper). A further dimension in which the use of surrogate end points of quality of life could be misleading is palliative care. The quality of the residual life at the end of life is a very important issue, and the dimension of quality of life has been widely investigated in the last years [37-39]. Quality of life assessment at the end of life is a very complex field of quality of life research, and the use of surrogate end points of quality of life is just one of the undefined aspects of this field. Progestins or corticosteroids are the drugs of choice in the palliative treatment of the cancer cachexia syndrome, and megestrol acetate or medroxyprogesterone acetate likely represent the gold standard to this aim. However, a recent systematic review highlighted that no significant improvement in quality of life besides weight gain or appetite improvement can be inferred from the trials investigating the role of megestrol acetate or medroxyprogesterone acetate in quality of life [40]. The reasons explaining the lack of improvement in quality of life assessment can be summarized as follows:

- Insufficient sensitivity of the instruments used for quality of life assessment (no validated instruments was used in the selected trials).

- Duration of the treatment and follow up too short to evaluate the impact of the treatment in overall quality of life.

- Secondary relevance of cancer cachexia in the status of terminal or pre-terminal patients.

Moreover, a further fundamental aspect is worthy to be underlined, as it is likely to concern not only cancer cachexia, but the most part of palliative care dimensions. Symptoms control probably represents an index of *activity* instead of *effectiveness*, and it can not be considered by itself a surrogate end point of quality of life without running the risk of drawing erroneous conclusions, as it is probably a relevant, but not fundamental dimension of quality of life assessment.

Conclusions

Surrogate end points are largely used in clinical research, and their use can not be considered wrong by a conceptual point of view. A surrogate end point is an useful index to evaluate a final outcome, as it is usually easier to be evaluated and is evaluable in a shorter time. Conversely, the use of a surrogate end point *instead of* a final outcome is wrong by a methodological point of view and can lead to draw misleading conclusions. Unfortunately, the use of surrogate end points in clinical research has gained ground in the last years, favouring a lot of conclusions that appear at least questionable when applied to daily clinical practice. Moreover, the use of surrogate end points as outcomes of effectiveness has been extended to survival and even to the assessment of quality of life. The use in

clinical research or clinical practice of surrogate end points such as clinical benefit or pain control is not a problem by itself. On the contrary, it should be worthy of renewed attention as concerns cancer-related symptoms and symptoms control. The actual problem is that the assessment of clinical benefit or pain is not used *with* quality of life assessment, but *instead of* quality of life assessment, and such an attitude inevitably reduces the quality of life dimension to mere symptoms control. Finally, reviewing the papers reporting data about quality of life assessment in oncology, some points can be highlighted:

- Quality of life assessment represents an independent outcome in clinical research and an index of effectiveness of a treatment.

- Surrogate end points of quality of life can represent an useful instrument in clinical research or daily clinical practice, on condition that they are used *with* and *within* quality of life assessment.

- The conclusions of trials using surrogate end points of quality of life *instead of* quality of life assessment as primary outcome should be evaluated with caution, and no definitive conclusion about quality of life should be drawn from such trials.

- The habit of regulators (FDA or EMEA) of using surrogate end points of quality of life to register new drugs should be handled with great caution, and further confirmatory data should be warranted before reaching a definitive confirmation.

The use of surrogate end points of quality of life can be useful within a project of quality of life assessment. On the other hand, the evaluation of quality of life using solely surrogate end points is incorrect by a methodological point of view and can lead to incorrect conclusions, that are just surrogate responses to surrogate questions.

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