



ACTUALIZACIÓN SOBRE LA CALIDAD DE VIDA EN EL PACIENTE CON CÁNCER DE PULMÓN NO MICROCÍTICO

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The goal of incorporating quality of life assessment into oncology trials is getting closer to being realized. Many studies now include quality of life evaluation; however, these are the minority of trials and the conduct of this assessment is often not ideal. The objective of this presentation is to outline briefly progress and pending questions in the incorporation of quality of life assessment into clinical trials and practice.

Although it may not be well recognized, both survival and quality of life are often directly related. That is, the status of the cancer affects both the length and quality of life. This inter-relationship between survival and quality of life is important. A recent analysis in non-small cell lung cancer demonstrated this finding clearly, and its implications are many. In that study, nearly 700 previously untreated patients were entered at 30 different centers into a randomized trial. If one looks only at baseline data, the most important pretreatment prognostic factor for survival is the quality of life score (in this case as determined by the patient using the LCSS instrument). Again, the quality of life score had a greater impact than stage (IIIB vs IV), performance status, or gender. While this may not be surprising to many, the implication of this finding is of great importance in study analysis of end points. That is, the attrition of patients within trials is not random. Those with poorer initial quality of life drop out of analysis (due to death or progression) significantly more rapidly. Thus, patients with poorer baseline quality of life but randomized to superior treatment arms in terms of survival, stay in a trial longer. This can paradoxically appear to elevate the quality of life of the group in the poorer surviving arm, since the patients with lower baseline quality of life drop out more rapidly. This is a factor that must be accounted for in randomized trials with different survival outcomes, and demonstrates some of the difficulties involved in the analysis of trials including this end point.

Can quality of life be defined sufficiently to be useful in clinical trials and practice? While defining quality of life can be controversial, most can agree on its components or dimensions. Quality of life, as a factor in health assessment, is generally thought of as being multidimensional. Common dimensions include physical, functional, psychological, social, and spiritual aspects. Each of these dimensions can be complex, but capturing information from all of these separates a quality of life analysis from an assessment of so-called "clinical benefit." Performance status scales (such as KPS or ECOG) are helpful measures that are often included in quality of life analysis, but are not replacements for it. Such single dimensional evaluations are valuable but do not encompass the multidimensional concept. There may be a role for each; however, the two should not be mistaken for each other.

Focusing on the reason for evaluating quality of life in a trial can help in the selection of the instrument used. Different instruments may try to capture each dimension in detail, or may concentrate on the dimensions likely to be affected by an intervention while assessing the others more globally. As quality of life analysis has evolved, so has the recognition for the need for different instruments. Such questionnaires have gone from the general, to disease-specific (cancer), to disease-site specific (lung cancer), and to treatment-specific (bone marrow transplant). It is reasonable for instruments to vary depending on the concepts or experiences they intend to capture. As an example, assessing quality of life a year after surgery in patients free of cancer may be somewhat different than measuring quality of life in patients with advanced stages of cancer under treatment with either of two chemotherapy regimens in a randomized trial. Both assessments can

be useful and many of the same considerations are shared. However, the differences between the two situations illustrates that one evaluation solution is unlikely to address all important issues. Many validated instruments are now available to match most needed applications.

Is there consensus on the methods for analyzing of quality of life data? The analysis presents several problems. First, most studies incorporate quality of life into clinical trials in which the primary endpoint is survival. The problem is that studies are often powered for the survival endpoint, which may not be sufficient to address quality of life considerations. Thus, the impact of an intervention on quality of life may be seen as a less valid evaluation, when in fact it is just as scientifically valid but suffers from having too few patients enlisted to properly address this aspect.

Another problem in analysis is that of multiple quality of life endpoints. Instruments use many questions to explore various dimensions of quality of life. It is curious that the criticism of evaluating many endpoints is often leveled at evaluations of quality of life, but is rarely raised when analyzing toxicity data. Indeed, a toxicity analysis of a new chemotherapeutic agent that failed to assess multiple areas, such as neutropenia, anemia, thrombocytopenia, hepatotoxicity or nephrotoxicity would be considered to be incomplete. As in any trial, the point of interest of the evaluation needs to be stated at the initiation of the trial. A global or summation quality of life score can be the major point tested while other aspects of interest are examined but are used to enhance the analysis - not replace it.

Quality of life assessments are troubled by missing data. These occur for two reasons. The first is that data may not be collected. The second is progression and death of patients with the disease. Statisticians have labored over models, which remain controversial, to correct for such missing data. Rather than search for such adjustments, more acceptable strategies are to consider the assessment interval as a part of the design, to emphasize with investigators the value of the quality of life issue, and to ascertain that these data are collected with the same vigor that imaging tests and blood studies are gathered. Failure to obtain CT scans is not tolerated in our studies evaluating response; nor is it acceptable to miss repeat quality of life assessments.

The second source of missing information occurs when a patient goes off study or when a patient dies. It has been shown that those patients with lower quality of life at the outset of a trial have a decreased survival, have poorer prognostic parameters, and drop out of studies earlier. Treatment may affect quality of life even after it is completed (such as the delayed effects of radiation therapy on pain relief or on radiation pneumonitis). It is important to continue assessment over the entire time in which the intervention may have an influence, or for the life of the patient. It may be more useful to envision the entire "amount" of quality of life of each patient in a trial, rather than examine quality of life at an arbitrary time (perhaps based on a chemotherapy schedule) in a trial.

How should quality of life data be presented? Is it important to know the percentage of patients with improvement or with stability? This too may vary according to the patient population. In patients with advanced disease in comparative trials, improvement may not be the best parameter; maintaining a reasonable level of quality of life may be desirable with a disease that is progressive when the quality of life was acceptable at the onset of treatment. Agreements on this type of analysis are necessary as we go forward with more trials including quality of life assessment. Presentations of results need to be clear and to focus on aspects with which all oncologists are familiar.

As with all oncology trials, design of the study has an impact on the interpretation of the results. Single arm uncontrolled studies of anticancer agents can help generate hypotheses; however, this design with quality of life endpoints can be even more difficult to analyze than the response or survival results. Typical supportive care will contribute to quality of life and palliative results in addition to the anticancer intervention, thus confounding the analysis. As difficult as using historical controls can be for response and survival results, it is even more so for quality of life in that few studies are available for comparison. Controlled phase III trials

have more value in this setting - as is true for survival results as well. Here too special problems exist in interpretation, especially when survival differences are found between the randomized arms due to non-random differential drop out rates.

Controversies continue as the evaluation of quality of life occurs as part of an increasing number of clinical trials. Illustrating the benefits and problems in analysis are phase II trials with pemetrexed and Iressa®. Results of randomized comparison trials are awaited to define clearly the quality of life impact of these agents. Phase III trials have demonstrated the palliative and quality of life benefits of docetaxel in both second line and first line settings.

As quality of life and clinical benefit assessments have become more frequent, the controversies are lessening. Agreement has been reached in defining and measuring quality of life. Consensus on methods of analyzing and presenting these endpoints is needed. Perhaps the largest challenge is to make the instruments easier to administer and use in daily practice. In the future, incorporating quality of life as part of daily oncology practice will enhance our treatment of malignancies. It is likely that with only a small amount of additional study, accurate evaluation of quality of life will become an integral part of cancer trials and cancer care.