Symposium article

Quality of life in lung cancer patients

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Summary

The quality of life of lung cancer patients is affected by several factors related to the patients, stage of disease and treatment characteristics. For small-cell lung cancer (SCLC), the treatment is generally aggressive, primarily based on chemotherapy. Treatment strategy for non-small-cell lung cancer (NSCLC) is strongly dependent on the stage of the disease and ranges from surgery to palliative chemotherapy. Over the last few years, very little progress has been made in terms of survival. Therefore, the effect of treatment on quality of life has become progressively more relevant. Among the instruments for measuring quality of life, there are some specifically developed for lung cancer, such as the European Organization for Research and Treatment of Cancer (EORTC) LC-13 questionnaire, the Functional Assessment of Cancer Therapy (FACT-L) questionnaire and the Lung Cancer Symptom Scale (LCSS). Up to now, few randomised clinical trials have correctly evaluated quality of life. There are evident pitfalls associated with the use of frequently non-validated tools, and poor methods of data analysis, but quality-of-life evaluation is crucial and should be addressed through well-planned and well-conducted prospective clinical trials.

Key words: non-small-cell lung cancer, quality of life, small-cell lung cancer

Factors of affecting quality of life in lung cancer

As with many other patients affected with solid tumors, the quality of life (QoL) of lung cancer patients is affected by several factors related to the patient, disease and treatment characteristics. Such determinants are correlated with the type and stage of disease affecting treatment strategy and different treatment strategies (e.g., surgery, radiotherapy, chemotherapy) determining patient acceptance and side effects.

For small-cell lung cancer (SCLC), the most widely accepted strategy is aggressive, primarily based on chemotherapy and combined with radiotherapy for a limited disease. On the other hand, the treatment strategy for non-small-cell lung cancer (NSCLC) is strongly dependent on the stage of the disease, surgery being the first choice for early stages, a combination of chemotherapy and radiotherapy for locally advanced disease, and chemotherapy alone being presently the best therapeutic option for metastatic patients.

Surgical resection, indicated in early stage NSCLC, implies a careful selection of patients based on the presence of co-morbidity, general health status and functional respiratory assessment. When feasible, the extension of resection may significantly impair patient QoL, e.g., in the case of pneumectomy. Combined chemotherapy and radiotherapy, employed for treatment of limited SCLC and locally advanced NSCLC, may produce significant toxicity, both acute (e.g., esophagitis, myelosuppression) and late (e.g., fibrosis), particularly when concurrent schedules are used; in addition, the logistics of concurrent, combined treatments are usually more complicated than single or sequential treatment strategies. In the case of prophylactic brain irradiation for limited SCLC, which was found to be effective in a meta-analysis of randomized clinical trials (1), the impact of toxicity (long-term neurological impairment) must be balanced, from the patient's perspective, with the chances of prolonging survival. Chemotherapy alone, employed for treatment of metastatic NSCLC and extensive SCLC, is frequently characterized by relevant toxicity, particularly when cisplatin is used or when combinations of several agents are applied. It must be acknowledged that, from the standpoint of toxicity, chemotherapy is usually viewed negatively by patients and relatives.

End points of lung cancer treatment

The treatment of SCLC does prolong patient survival in comparison with no treatment, independently of stage of disease. It produces relatively high rates of tumor regression that have a positive impact on tumor-related symptoms. However, no major progress has been made during the last decade, and several schemes of chemotherapy, including the oldest ones, are similarly active and effective. Thus, it may be argued that if no difference in prolonging survival exists among different schemes, their toxicity and impact on QoL should be considered in clinical practice. Thus, QoL should also be an impor-
tant end point in clinical trials evaluating treatments that a priori have no more chance of prolonging survival than standard ones.

For early stage NSCLC patients, cure is a possible end point of treatment; unfortunately, only about the half of such patients are actually saved by surgery alone. Thus, adjuvant and neoadjuvant chemotherapy are actually being studied, with the aim of measuring their possible impact on patient survival. From this standpoint, short-term QoL seems to be a secondary end point. For locally advanced NSCLC, the standard strategy is based on a combination of chemo- and radiotherapy. However, the manner of the combination (concurrent or sequential), the type of drugs, the radiotherapy dose and schedule are all investigational both in terms of patient survival and of QoL. In metastatic NSCLC, chemotherapy has only palliative effects; its impact on survival is modest [2] and cisplatin induces toxicity and patient discomfort. Thus, in this stage of disease, QoL should more frequently be considered as a primary end point of treatment both in clinical practice and, more importantly, in clinical trials. Indeed, when patient preferences have been assessed, it has been shown [3] that the degree of expected toxicity does significantly affect the minimum survival gain as patients regard the effects of toxicity to be a reason for not accepting chemotherapy. In the same study, when patients were informed of a possible three-month survival prolongation, only one-fifth of the patients accepted chemotherapy. On the other hand, two-thirds of the patients opted for chemotherapy in the scenario in which this form of therapy demonstrated no effect on survival but provided significant reduction of pain and other tumour-related symptoms.

**Specific problems of QoL evaluation in lung cancer**

QoL analysis in lung cancer is affected by some general sources of biases that become particularly important due to epidemiological and prognostic specificities of the disease.

First of all, lung cancer is frequently diagnosed in elderly patients. This implies both cultural problems, illiteracy still being a problem in many parts of the world for people born at the beginning of the 20th century, and medical problems, because of co-morbidities frequently affecting elderly patients and potentially biasing QoL evaluation. Second, the short-term survival of advanced lung cancer patients and the rapid deterioration of performance status produce problems in collecting QoL questionnaires; this leads to frequent but not necessarily random occurrences of missing data. Indeed, it has been shown that the baseline QoL estimates are worse for those patients who subsequently fill in a few questionnaires as compared to those who are fully compliant with QoL assessment until the end of treatment [4].

**Specific instruments for QoL evaluation in lung cancer**

Among the instruments for the evaluation of QoL, there are some specifically developed for lung cancer. The European Organization for Research and Treatment of Cancer (EORTC) LC-13 questionnaire, a list of symptoms usually administered together with the core C-30 questionnaire, is the most widely used in clinical trials. The Functional Assessment of Cancer Therapy (FACT-L) questionnaire has a similar structure of 41 items in total, concerning both general health status and site-specific symptoms. The Lung Cancer Symptom Scale (LCSS) is a list of nine site-specific symptoms, evaluated by the patient, and six symptoms evaluated by an external observer; no items in this scale are related to the evaluation of treatment-induced toxicity [5].

**QoL evaluation in NSCLC randomised clinical trials**

To date there have been no published papers dealing with QoL evaluation in the adjuvant treatment of NSCLC. In a recently completed adjuvant Italian trial (Adjuvant Lung Project Italy – ALPI), a QoL assessment was planned in a satellite project, but it was not successful because of low compliance by participating centres.

In locally advanced disease, QoL has been assessed in only one randomized trial [6] of radiotherapy vs. radiotherapy + chemotherapy. Unfortunately, compliance was very low, with 67 out of 446 patients evaluable for QoL measured by the EORTC questionnaires; thus, no conclusion can be drawn.

On the contrary, formal QoL evaluation was done in many randomized clinical trials performed in advanced NSCLC, although it was indicated as the primary end point of the study in only two cases [4,7].

Several studies have dealt with a comparison of chemotherapy to best supportive care [4, 6, 8–13]. The number of patients enrolled in these studies ranged from 48 to 351, although compliance with QoL analysis was never complete. In addition, some of these studies were flawed by inappropriate methods of analysis and some of them have not yet been published as extended papers. The ELVIS (Elderly Lung cancer Vinorelbine Italian Study) group, coordinated by our institution, organised the first randomised trial dedicated to advanced NSCLC patients over 70 years old, comparing vinorelbine to best supportive care. In that study, QoL evaluated by EORTC C-30 and LC-13 was the primary objective because the investigators thought that a significant impact of single agent vinorelbine on survival was not probable. To their surprise, the treatment significantly prolonged survival (28 vs. 21 weeks of median survival) to the same extent observed with cisplatin-based chemotherapy in adult patients, as reported by the meta-analysis [2]. Patient compliance with QoL assessment was high on the baseline questionnaire (91.6%) and progressively decreased (39.0% on the 6th questionnaire). The longer survival in the vinorelbine arm meant
that patients in this group completed more questionnaires than those in the control arm. A pattern of missing data was dependent on baseline values and time of the QoL assessment. It was shown that patients with a lower baseline global health status score tended to drop out of the study earlier than those with a higher score, and the probability of their dropping out was related to previously observed scores. Furthermore, the global health status of subjects who no longer provided QoL assessments had worsened by the time of the previous available observation. Vinorelbine induced an overall improvement on the functional scales (Figure 1), which was statistically significant for cognitive function and borderline for global health status. Furthermore, patients treated with vinorelbine had higher scores than control patients for some lung cancer-specific items (pain, dyspnoea) but they scored lower for treatment-related toxicity items (constipation, nausea and vomiting, hair loss, and peripheral neuropathy), as shown in Figure 2.

Many studies comparing different chemotherapy regimens have dealt with QoL analysis [7, 14-19]. Two large randomised trials showed a difference in QoL (measured by EORTC scales) favouring cisplatin + paclitaxel over cisplatin + VM26 [16] and over cisplatin alone [15]. In both studies the survival rate was the same; thus, the advantage of QoL could be crucial to the interpretation of study results. An ECOG trial comparing cisplatin + paclitaxel (2 different doses) to cisplatin + etoposide found a statistically significant survival advantage for paclitaxel-containing regimens, with no difference in QoL, measured by the FACT-L scale [17]. Other studies failed to demonstrate any difference in QoL and survival between the compared arms. As a criticism of these trials, one can consider that the treatments under study were not very different from one another in terms of potential toxicity; indeed, in most of these studies cisplatin was present in both arms [18, 19]. A challenge for the future is to determine whether non-cisplatin-based chemotherapy provide better QoL outcomes with similar survival and less toxicity than standard cisplatin-based treatment.

**QoL evaluation in SCLC randomised clinical trials**

Many trials have been conducted on SCLC in the last few years, addressing questions like duration of chemotherapy, feasibility of oral treatment, efficacy of intensified chemotherapy, the role of 'new generation' drugs in second-line treatment and supportive care benefit concomitant with chemotherapy. Some of these trials have also had quality of life as a primary objective.

The effect of the duration of chemotherapy on QoL was investigated in a randomised trial [20] of 458 patients with extensive disease SCLC. The trial compared six cycles of the ECMV regimen (etoposide, cyclophosphamide, methotrexate, vincristine) to three cycles of the same regimen and to six cycles of IE (ifosfamide, etoposide). There was no difference in terms of toxicity, response rate, survival, symptom palliation and QoL among the three arms. Symptom control (cough, haemoptysis, chest pain, anorexia and dysphagia) was achieved by 63% of the patients overall. These results confirmed the ineffectiveness of a long-lasting treatment for extensive disease SCLC.
Oral etoposide has been proposed for the treatment of unfit patients ineligible for standard polychemotherapy. Two large randomised studies [21, 22] compared oral etoposide to standard intravenous (i.v.) chemotherapy. Even if doses and schedules of oral etoposide and standard chemotherapy regimens were different in the two studies, the results of both studies were equivalent: standard i.v. chemotherapy proved more effective than oral etoposide in terms of survival. As for QoL, no difference was found by Girling et al., using an ad hoc questionnaire. On the contrary, in the study of Souhami et al., all aspects of symptom control and QoL evaluated by the Rotterdam Symptoms Scale and a Daily Diary Card were either the same or worse in the oral etoposide group.

The inclusion of QoL evaluation among the end points of clinical trials has to be considered crucial for studies dealing with dose-intensive chemotherapy, due to treatment-induced toxicity. Dose-intensive chemotherapy is a priori considered as possibly more effective but more toxic than standard treatment. A recent randomised trial [23] comparing standard CAE (cyclophosphamide, adriamycin, etoposide) with intensive CAE (doses increased by 50%, interval between cycles shortened to 14 days, with G-CSF support) showed a slightly longer survival for patients receiving intensive treatment (one-year survival: 47% vs. 39%, P < 0.04); and, remarkably, haematological toxicity was lower in the intensive arm thanks to prophylactic G-CSF. QoL analysis, using a modified version of the Rotterdam Symptoms Scale, showed no difference between the two arms. These results suggest that some form of intensive chemotherapy can be an effective option in the treatment of SCLC without worsening QoL.

Among randomised trials evaluating new drugs for SCLC treatment, a relevant contribution in terms of QoL was made by von Pawel et al. [24]. In 211 patients with recurrent SCLC, they compared a topotecan to a standard CAV regimen; symptom control was an objective of the study. The two regimens produced similar survival, response rates, and duration of response. Topotecan induced more thrombocytopenia and anaemia but less asthenia, cardiotoxicity and neurotoxicity. An evaluation of symptom control, attained by using an ad hoc questionnaire, showed significant benefits with topotecan in dyspnoea, anorexia, asthenia and global health status. Following this trial, topotecan was approved by the US Food and Drug Administration for use as second-line treatment in SCLC as a result of its palliative efficacy.

In the area of supportive care, megestrol acetate administration (800 mg/d) concomitant with chemotherapy using cisplatin and etoposide was compared to chemotherapy alone [25]. Megestrol led to weight increase and reduced anorexia in a higher proportion of patients, and resulted in a lower incidence of nausea and vomiting; as negative effects, it caused a higher incidence of oedemas and thromboembolic episodes. Surprisingly, the response rate was lower in patients receiving megestrol. QoL data, measured by a visual analogue developed by the authors, showed that megestrol acetate did not produce any significant improvement of the investigated items. Thus, the authors did not recommend the routine use of megestrol acetate with chemotherapy in SCLC. Unfortunately, the use of a non-validated tool for QoL analysis does not allow a definitive conclusion.

Conclusions

Over the past few years, very little progress has been made in the treatment of lung cancer patients in terms of increased survival. As a consequence, the effect of treatment on QoL has become progressively more important when discussing treatment options with patients. Sadly, few randomised clinical trials have correctly evaluated QoL. Improving the quality of our knowledge of the impact of available treatments on patient QoL is mandatory and can be addressed only through well-planned and conducted prospective clinical trials.

References

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