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Quality of life in lung cancer patients: the way forward

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Despite important treatment progress, lung cancer, often diagnosed as advanced disease, is still characterized by a poor prognosis. Quality of life (QoL) evaluation, defined as the patients' perception of physical, psychological and social impact of cancer and its treatment, plays a central role, together with the "classical" endpoints of efficacy and safety, to understand the real value of a treatment, its potential risks and benefits.

Within a scenario of rapid development of novel therapies, accelerated access to treatments and surrogate endpoints for drugs approval, regulatory agencies - as the US Food and Drug Administration and the European Medicines Agency - have emphasized the significance of QoL evaluation in clinical trials, underlining the importance of patients' perception as a defined outcome measure.^{1,2} Scientific societies - like American Society of Clinical Oncology and European Society for Medical Oncology - have drawn up specific frameworks to determine the value of oncological treatments, including QoL, to define the final assigned score.^{3,4}

However, despite its universally recognized value, QoL role seems still marginal.⁵ In a recent literature analysis, QoL was not assessed in a relevant proportion of lung cancer phase III trials, with significant under-reporting of results in primary publications, even in the advanced/metastatic setting and in trials with a surrogate primary endpoint.⁶

Actually, QoL methodology still represents a challenge, and choice of questionnaire, timing of administration and modality of analysis are quite heterogeneous.⁷ The general European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the specific Lung Cancer 13 (QLQ-LC13) module are among the most used instruments.⁶ Obviously, to remain effective tools, QoL questionnaires should be in line with treatment progress. Since 1994, when QLQ-LC13 was developed⁸, considerable progresses have been reached in the management of lung cancer patients. Furthermore, targeted therapies, immunotherapy, combination strategies have a completely different toxicity profile. In *The Lancet Oncology*, Koller and colleagues

present the psychometric properties of the EORTC QLQ-LC29, the update of LC13, precisely developed with the aim of containing the emerging QoL items and toxicities (although not specifically listing all the most common immune-related symptoms). It consists of 29 items (12 preserved from QLQ-LC13), and includes 15 single items and 5 multi-item scales (coughing, shortness of breath, hair problems, fear of progression, and - optional- surgical symptoms).⁹ All patients filled in the questionnaire at the first time-point and half of them at a second time-point too.

In lung cancer patients, symptoms can rapidly change, either in terms of improvement due to treatment efficacy or in terms of worsening when the treatment is ineffective and/or toxic. When authors asked patients, 2-4 weeks after the first questionnaire, if they were getting better, worse or stable, only 41.5% declared to be stable.

As expected, there was a significant association of most questionnaire scores with patient's performance status. However, when these instruments are used within interventional clinical trials, patients are strongly selected, and their symptom burden at baseline is reasonably lower compared to patients treated in clinical practice.

Consequently, information acquired with early QoL evaluation is useful, more than to describe treatment efficacy, especially to exclude increased toxicity. On the other hand, treatment efficacy in terms of QoL benefit and symptom control can be effectively captured analyzing time-to-deterioration¹⁰. The latter analysis allows to focus the attention later in QoL trend, while the description of treatment failure within clinical trials has been traditionally based on instrumental disease progression only.

For all QoL analyses, the definition of "minimal important difference" (MID) is actually crucial. Koller and colleagues acknowledge the absence of MID definition as one of the main limitations of their work. Whichever the modality of presentation of results (mean changes, proportion of responders, time-to-deterioration), as for other endpoints, clinical

relevance of QoL differences should always be considered, beyond statistical significance. As the original 1994 version until now⁶, QLQ-LC29 will be reasonably used in many clinical trials, and a proper interpretation of results needs MID definition.

Despite the availability of several instruments, now enriched by the new EORTC QLQ-LC29, QoL has been too often considered a “Cinderella” outcome⁷, even in a setting like lung cancer. However, despite methodological issues, importance of QoL results in the definition of treatment value, within a patient-centered approach, is definitely increasing. The publication in *The Lancet Oncology*, a reference journal for clinical cancer specialists, of the psychometric properties of the QLQ-LC29, witnesses this strategic change.

All stakeholders (sponsors, researchers, patients, regulatory agencies and scientific journals) should encourage QoL inclusion among study endpoints and reporting of QoL results in scientific publications.

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