Quality of life: an important element of treatment value

Quality of life results: a fine dowel in the mosaic of treatment value.

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In the era of platinum-based chemotherapy, the attempt of improving quality of life (QoL) of patients with advanced non-small cell lung cancer (NSCLC) using a less toxic treatment was often disappointing. In a randomized trial comparing cisplatin-based treatment to a “platinum-free” combination, although the latter was associated with a significantly reduced amount of toxicity and an improvement in some specific QoL items, the primary endpoint of improving global QoL was not met [1]. The lesson was that, in patients suffering from a disease often associated with relevant symptoms, reduction of treatment-related toxicity in itself is not enough to improve global QoL, and a better control of disease is needed to shift the QoL balance.

In recent years, randomized trials comparing tyrosine kinase inhibitors with platinum-based chemotherapy in patients with oncogene-addicted advanced NSCLC have repeatedly demonstrated that, in a properly selected population, different efficacy of treatments can produce a relevant difference in patients’ QoL [2-4]. Now, a similar benefit has been shown within a randomized trial comparing the immune checkpoint inhibitor pembrolizumab with platinum-based chemotherapy as first-line treatment of patients with advanced NSCLC, selected for the expression of programmed death ligand 1 (PD-L1) on at least 50% of tumor cells [5]. Primary results of the trial were published in 2016: pembrolizumab was associated with a significant prolongation in progression-free survival (primary endpoint) and overall survival, and with fewer adverse events [6]. Evaluation of patient-reported outcomes was an exploratory endpoint, and it was not included at all among the results presented in the primary publication. In the article by Brahmer *et al.* now published in The Lancet Oncology, pembrolizumab was significantly better than platinum-based chemotherapy in terms of both improvement in global QoL scores and time to deterioration of tumor symptoms (cough, dyspnea, chest pain) [5]. From a methodological point of view, proper analysis, presentations

and interpretation of clinical relevance of QoL data is not easy, particularly in settings like advanced NSCLC, where the number of missing questionnaires is not negligible, and most missing data are not at random, being related to disease progression and worsening of patient's conditions [7].

Given the already known benefit in efficacy and in toxicity, the significant difference in global QoL favoring pembrolizumab over platinum-based chemotherapy is not surprising. Primary publication of the trial (including progression-free survival, overall survival, objective response rate and toxicity data) was already sufficient to convince scientific community about the relevance of the clinical results obtained with pembrolizumab in these patients. However, even when the experimental treatment demonstrates a clinically relevant improvement in survival endpoints, patient-reported outcomes and QoL results are still of interest, allowing a more complete definition of benefits and harms associated with treatment [8]. It is not surprising that both the framework proposed by the American Society of Clinical Oncology (ASCO) [9] and the European Society of Medical Oncology (ESMO) magnitude of benefit scale [10] evaluating the value of anticancer treatments include QoL results among the parameters considered for the evaluation of study results. Namely, in the ASCO framework, a "palliation bonus" (10 points) is awarded by the experimental treatment, if a statistically significant improvement in cancer-related symptoms is shown, and a "QoL bonus" (10 points) is awarded if a statistically significant improvement in QoL is demonstrated [9]. Similarly, in the ESMO scale, preliminary scores based on treatment efficacy can be upgraded when the experimental arm demonstrates improved QoL or delayed deterioration in QoL (or substantial reduction in severe toxicity) [10].

Based on these tools, a complete evaluation of treatment value can be properly made only if scientific community could evaluate QoL results at the same time of the other

trial endpoints [8]. The ancillary paper dedicated to QoL results obtained with first-line pembrolizumab is being published almost 1 year later than the primary publication. Admittedly, this delay is common for many trials, although it would be desirable that QoL results were available along with the primary publication, to allow a timely evaluation of the benefit / risk ratio and of the value of the treatment.

The recent update of ASCO clinical practice guidelines [11] includes a strong recommendation that, in the absence of contraindications to immune checkpoint therapy, single-agent pembrolizumab should be offered as standard treatment to patients with both non-squamous and squamous NSCLC, characterized by high PD-L1 expression. The results by Brahmer *et al.*, showing a clear benefit in QoL, reinforce the evidence supporting pembrolizumab as first-line treatment of patients with advanced NSCLC selected for the expression of PD-L1 on at least 50% of tumor cells.

Conflicts of interest statement

Massimo Di Maio acted as consultant for AstraZeneca, Bayer, Janssen, Bristol Myers Squibb, and Eli Lilly, and received speaker's fee from Merck Sharp & Dohme.

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