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Availability of quality-of-life results for clinical decisions: an evolving scenario

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Attention to patient-reported outcomes and health-related quality of life (QoL) as an endpoint in clinical trials in oncology is constantly rising.[1] In principle, data collected, analysed and presented within clinical trials have both scientific and regulatory implications.[2] Although recently defined a 'Cinderella' outcome,[3] the availability of QoL results can contribute to the definition of treatment value[4] and can inform communication with patients.[5]

The study by Gupta and colleagues focused on QoL data in 233 clinical trials conducted in haematology and oncology, corresponding to 207 treatments approved by the US Food and Drug Administration in a 5-year period between 2015 and 2020.[6] Many of their findings do confirm what has been described in similar studies: often, at the moment of regulatory approval and subsequent availability of treatment in clinical practice, the scientific community does not have QoL data, either because QoL was not included among endpoints or because collected data are still not published.[1 7] Namely, Gupta and colleagues found that QoL was included among endpoints in 55.8% of the trials and was reported in 50.2%. QoL data were first reported in the primary publication in only 30% of trials.

Within the 5-year period analysed, the authors did not find a significant time trend in QoL reporting. The period analysed was probably too short to observe relevant changes. However, in a previous analysis of oncology publications encompassing a 10-year period between 2012 and 2021, we described an improvement in the inclusion of QoL into clinical trials.[1] Nevertheless, there was an opposite trend in the reporting of QoL results in primary publications (which was even worse in 2017–2021 compared with the previous 5 years), so the chance of reading QoL results in a primary publication of an oncology trial was substantially the same over the time.

Of note, Gupta and colleagues did not simply describe the availability of QoL outcomes but went into detail about the type of outcome. How many times has a treatment approved for use been shown to improve patients' QoL? Unfortunately, this improvement is demonstrated only in a minority of cases. As a general rule, the opportunity to read and discuss with colleagues and patients the QoL results obtained by treatments available in clinical practice is particularly useful. When the experimental treatment has shown a benefit in terms of overall survival (OS), it is important to know if patients will live better in addition to living longer and if the prolongation of life expectancy comes at the price of a QoL worsening, for instance, due to increased toxicity. In the analysis by Gupta and colleagues, we can read that when the approval was based on OS benefit, an improvement in QoL was actually demonstrated only in 34% of trials. Even more importantly, when the experimental treatment has shown a benefit in terms of a surrogate endpoint (typically a prolongation in progression-free survival, which means instrumental disease control), it is crucial to know if that instrumental benefit is associated with QoL improvement and prolongation of time to QoL deterioration. Well, when the approval was based on a surrogate endpoint, only 17.9% of trials (28.4% considering only progression-free survival and disease-free survival) did actually show a QoL improvement. It goes without saying that these figures are largely suboptimal.

Calling for greater attention to QoL when drafting protocols (including QoL among endpoints) and when publishing results (presenting QoL details in the primary publication) does not mean denying the existence of a number of challenges in the methodology. Gupta and colleagues defined the positivity of QoL results looking at the impact on the global domain of the assessment tool, where available. However, differently from

the analysis of the primary endpoint, which is reasonably based on a predefined hypothesis, QoL analysis is exploratory in the vast majority of cases, and the interpretation of QoL results is not necessarily easy. Global domain (eg, items 29–30 of the EORTC QLQ-C30 questionnaire) is not necessarily a sensible synthesis of the whole instrument, and there could be clinically relevant differences in other items and scales, even in the absence of a significant difference in global status. Furthermore, the authors declared that due to remarkable heterogeneity between the studies analysed, the determination of QoL positivity was based on statistical rather than clinical significance. This means that, in some cases, QoL differences among treatments could be negligible and not necessarily clinically relevant: when presenting and when reading the results, the minimum clinically important difference should always be considered to allow a meaningful interpretation.

Gupta and colleagues deserve credit for having reminded the scientific community of the need to keep the bar high by including QoL among the parameters necessary to define the value of a cancer treatment. Invoking the availability of results is only the first step. A clear demonstration of benefit would be desirable to consider the value of the treatment high. I believe that many oncologists are more familiar with 'traditional' investigator-reported endpoints, like objective response rate, progression-free survival and OS but probably less familiar with the correct reading and interpretation of QoL results. Now is the time for authors, editors and the entire scientific community to stimulate education on the correct analysis, reading and interpretation of QoL data.

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