

Time to health-related quality of life score deterioration in oncology phase III clinical trials: a systematic review

Emilie Charton¹, Fabio Efficace², Francesco Cottone², Célia Touraine³, Benjamin Cuer^{3,4}, Zeinab Hamidou^{5,7}, Frédéric Fiteni^{3,6}, Franck Bonnetain^{1,7}, Caroline Bascoul-Mollevi^{3,4,7}, Amélie Anota^{1,7}

¹ Methodology and Quality of Life Unit in Oncology, INSERM UMR 1098, University Hospital of Besançon, Besançon, France.

² Data Center and Health Outcomes Research Unit, Italian Group for Adult Hematologic Diseases (GIMEMA), Rome, Italy.

³ Montpellier Cancer Institute (ICM) – Val d’Aurelle, University of Montpellier, Montpellier, France.

⁴ Institute of Cancer Research of Montpellier (IRCM), ICM, INSERM, Montpellier, France.

⁵ EA3279 Self-perceived Health Assessment Research Unit, Aix-Marseille University, Marseille, France.

⁶ Department of Medical Oncology, University Hospital of Nîmes, Nîmes, France.

⁷ French National Platform Quality of Life and Cancer, Besançon, France.

Background The time to deterioration (TTD) has been proposed as a modality of longitudinal analysis of patient-reported outcomes (PROs) in oncology randomized clinical trials (RCTs). Recommendations on this approach were suggested and adapted to the cancer context (adjuvant or advanced setting) according to: the reference score, the event definitions and the minimal clinically important difference (MCID) (Anota A. et al *QoL Research* 2013). The aim of this review was to assess how the TTD was defined and reported in phase III RCTs since 2014.

Method A systematic review was performed in PubMed/Medline to identify studies published between January 2014 and April 2018. All phase III RCTs in oncology including a PRO endpoint with the TTD approach were considered. We collected general information about the study, PROs assessment and TTD approach, such as the event definition, the choice of reference score, the MCID and whether the deterioration was definitive or not. We focused in particular on missing data and how death was handled.

Results A total of 311 articles were screened and 36 studies (11.6%) were finally identified as relevant according to predefined criteria. Among these 36 studies, 31 (86.1%) were on metastatic or advanced setting. Twelve studies (33.3%) clearly reported that patients without baseline scores were excluded from TTD analyses. The deterioration was defined as definitive in 8 studies (22.2%) and confirmed in 7 studies (19.4%), which corresponds to a deterioration maintained over time and sustained for a defined time period, respectively. The baseline score was explicitly stated as the reference score to

qualify the deterioration for most of studies (n=30, 83.3%). Composite definitions of PRO deterioration were considered in 15 studies (41.7%), including deterioration in several PROs scales (6.7%) and either death (53.3%) or simultaneously death and disease progression (33.3%) in the event definition.

Conclusion This review highlighted the lack of standardization of the TTD approach, despite the recommendations already proposed. A better attention is required to the definition of deterioration, depending on the cancer setting. In particular, in case of composite definition, the event associated should be meaningful in term of clinical benefit for the patient.

Funding Institut National du Cancer (INCA 11862)