TIME TO DETERIORATION (TTD) IN HEALTH RELATED QUALITY OF LIFE (HRQoL) IN NSCLC PATIENTS: A REVIEW OF DEFINITIONS

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INTRODUCTION

- Time to deterioration (TTD) in HRQoL as collected by means of Patient Reported Outcomes (PRO) is now considered a common longitudinal analysis for HRQoL data in oncology trials. Among its advantages are its ability to deal with missing data by making assumptions and to address the potential occurrence of a response shift effect.
- Different definitions can be used depending on disease stage, expected impact of the disease, and treatment received. Events can be defined in relation to a reference score, clinically meaningful threshold, missing scores, including death/progression or not.
- However, there are currently no recommendations or consensus in this regard, with the result that TTD reflects heterogeneity[1].
- This is a targeted literature review of the TTD definitions used in Non-Small Cell Lung Cancer (NSCLC) trials.

METHODS

- A search in clinicaltrials.gov was performed with the following terms: **"NSCLC, quality of life"** and applying the filter for **completed studies**. Only studies with completion date from January 2013 onwards or blank were selected for review.
- Study results for the selected studies were searched on clinicaltrials.gov, PubMed, Annals of Oncology and websites of ASCO, ESMO and NICE.
- The disease stage, treatment line, PRO instruments used, TTD definition, threshold for deterioration and censoring rules were abstracted and summarised.

RESULTS

- We identified 244 studies, of which 85 meet the selection criteria for completion date. Sixteen (16) reported having performed TTD analyses. All 16 studies included patients with stage III, IV or recurrent NSCLC.
- The exact definition of TTD was provided in 14 studies (see table below for details), while the other 2 did not specify the exact definition applied.
- The PRO instruments used were: EORTC QLQ-LC13 and QLQ-C30 in 9 studies, LCSS in 5 studies and FACT-L in 3 studies. Some studies collected more than one PRO instrument.
- Among those studies reporting at least partly the definition used, 12 used time to first deterioration without confirmation required, 2 required confirmation, 3 used a composite endpoint of deterioration in one of several symptoms, and 6 included death as an event. Disease progression was not defined as an event in any study. Definitive deterioration was not defined in any study.
- All deteriorations were calculated with respect to baseline.
- Eight studies described the censoring rules for TTD.
- Reported thresholds were 10 points (pts) for QLQ-C30, 10 and 5 pts for QLQ-LC13, half SD at baseline/10 mm/15mm for LCSS, 6 pts for FACT-L total score, 1.5 and 3 pts for LCS and 6 pts for FACT-L TOI.

Study ID (acronym)	Study design	NSCLC stage	Treatment line	Hierarchy position for PRO endpoint	PRO instrument*	TTD definition		Threshold	Statistically significant differences	
						Event	Composite endpoint		PRO endpoint	Primary endpoint
NCT00883779 (FASTACT-2)	RCT, DB, Ph III	IIIB or IV	1L	Secondary	FACT-L	First	Death	Total+TOI: 6 points LCS: 3 points	Y, all assessed endpoints	Y (PFS)
NCT01351116 (BRACHY)	RCT, OL, Ph III	III, IV or recurrent	1L	Secondary	LCSS	First	Death	10 mm	No results available	NA (HRQoL)
NCT01017874	RCT, OL, Ph III	IIIB or IV	1L	Secondary	LCSS	First	N	½ SD	Loss of appetite and Pain	N (PFS)
NCT00981058 (SQUIRE)	RCT, OL; Ph III	IV	1L	Secondary	LCSS	First	N	15 mm	N	Y (OS)
NCT01121393 (LUX-LUNG 6)	RCT, OL, Ph III	IIIB or IV	1L	Secondary	C30/LC13	First	Death	10 points	Cough, Dyspnea, Pain	Y (PFS)
NCT02142738 (KEYNOTE 024)	RCT, OL, Ph III	IV	1L	Exploratory	C30/LC13	Confirmed	Several symptoms	10 points	Y	Y (PFS)
NCT00556322 (TITAN)	RCT, OL, Ph III	III, IV or recurrent	2L	Secondary	FACT-L	First	Death	Total: 6 points LCS: 1.5 points	N	N (OS)
NCT01168973 (REVEL)	RCT, DB, PBO-control, Ph III	IV or refractory	2L	Secondary	LCSS	First	N	15 mm Sensitivity: 10 mm	N	Y (OS)
NCT01871805 (NP28761)	Single arm, Ph II	IIIB or IV	2L	Secondary	C30/LC13	First	Several symptoms	10 points	NA Single arm study	NA (ORR)
NCT02151981 (AURA3)	RCT, OL, Ph III	IIIB or IV	2L	Secondary	C30/LC13	First	Death	10 points	Chest pain, dyspnea	Y (PFS)
NCT02094261 (AURA2)	Single arm, Ph II	IIIB or IV	2L	Secondary	C30/LC13	First	Death	C30: 10 points LC13: 5 points	NA Single arm study	NA (ORR)
NCT01085136 (LUX-Lung 5)	RCT, DB, Ph III	IIIB or IV	2L+	Exploratory	C30/LC13	First	N	10 points	N	Y (PFS)
NCT01360554 (ARCHER 1009)	RCT, DB, Ph III	III or IV	2L+	Secondary	C30/LC13	Confirmed	Several symptoms	10 points	N	N (PFS)
NCT01529112 (E7080-703)	RCT, DB, PBO-control, Ph II	III or IV	3L+	Exploratory	C30/LC13	First	N	10 points	Dyspnea	N (OS)

Abbreviations: C30/LC13: EORTC QLQ-C30 and lung cancer module; DB: double blind; OL: open label; LCS: Lung Cancer Subscale; LCSS: Lung Cancer Symptom Scale; N: No; NA: Not applicable; NSCLC: non-small cell lung cancer; PBO: placebo; Ph: phase; RCT: randomised clinical trial; TOI: Trial Outcome Index; Y: Yes
*__Assessed outcomes__ LCSS: 6 symptoms (loss of appetite, fatigue, cough, dyspnea, hemoptysis, pain) and 3 global measures (interference with normal activity, quality of life, overall lung cancer symptoms) / FACT-L: Total score, TOI, LCS / C30: 5 functional scales (physical, role, cognitive, emotional, social), 3 symptom scales (fatigue, pain, nausea/vomiting), 5 individual items (dyspnea, loss of appetite, insomnia, constipation, diarrhea) and global health status/QoL scale / LC13: 4 lung-cancer symptoms (cough, hemoptysis, dyspnea, site-specific pain), 4 treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy, alopecia) and 1 item on pain medication

DISCUSSION

Our research showed that only 18% of the studies collecting HRQoL data perform TTD analysis, despite its advantages in dealing with missing data, death and response shift, as well as providing clinically interpretable results[2]. Time to first HRQoL deterioration without confirmation of the event was the most frequent definition identified, regardless of the treatment line. Only one study performed sensitivity analysis around the threshold and none reported sensitivity analyses around the event definition.

There are recent initiatives to standardize PRO analyses[3], including TTD, however, to date no specific guidance has been published. Current thinking is that extensive sensitivity analyses should be conducted around the threshold, censoring rules, as well as event definition, i.e. first/confirmed/definitive deterioration[1,2,3]. Our research demonstrated that current practice is not aligned with this thinking.

1. Anota et al Qual Life Res (2015) 24 / 2. Bonnetain et al. JCO (2016) 34 (16) / 3. Bottomley et al. 2016 Lancet Oncology

International Society for Pharmacoeconomics and Outcomes Research, 21th Annual European Congress, poster presentation