Time to health-related quality of life improvement as a key outcome in modern anticancer therapies

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Abstract

Objective

Major advances have recently been made in the treatments of cancer, which now also have the potential to improve patients' health-related quality of life (HRQOL). We propose the Time To HRQOL Improvement (TTI) and the Time To Sustained HRQOL Improvement (TTSI) as potentially important cancer outcomes to be used in longitudinal HRQOL analyses.

Study Design and Setting

As proof of principle we defined TTI and TTSI, using the Fine-Gray model to include competing risks in estimates, in a case study in real life of a cohort of newly diagnosed cancer patients receiving a targeted therapy. HRQOL was evaluated before and during therapy with six assessments over a 24 months period, using the well validated EORTC QLQ-C30 questionnaire.

Results

For each assessed HRQOL domain, we assessed TTI and TTSI and estimated the cumulative incidence of either temporary or sustained patients' clinically meaningful improvements, also accounting for the occurrence of competing events.

Conclusion

TTI and TTSI are potentially important outcomes in the era of modern anticancer therapies. The analysis of TTI and TTSI by competing risks approach will further add to the statistical methods that can be used to inform on the impact of cancer therapies on patients' HRQOL.

Keywords

Time to HRQOL improvement; Time to sustained HRQOL improvement; Competing risks; Health-Related Quality of Life; Targeted therapies; Immunotherapy; Cancer.

What's new

- Modern anticancer therapies remarkably improved clinical outcomes for several cancer populations, making the improvement in health-related quality of life (HRQOL) a more frequent possibility.
- We propose time to HRQOL improvement (TTI) and the time to sustained improvement (TTSI) as potentially important outcomes of interest in cancer research, including definitions, estimation methods and reporting procedures.
- We present and recommend the use of the Fine-Gray model to define and estimate TTI and TTSI, to account for competing events and allowing for a great adaptability to specific clinical settings and study designs.
- We introduce and describe the concept of competing HRQOL measures in achieving the earliest improvement, either temporary or sustained.

1. Introduction

Health-related quality of life (HRQOL) is a multidimensional construct reflecting self-perceived well-being, in relation to any health issue[1]. Evaluation of HRQOL and other patient-reported outcomes (PROs) is now highly valued by regulatory stakeholders[2-5] and is critical in cancer research to complement more traditional outcomes, e.g overall survival (OS), so as to better inform patient care[6].

Several examples exist of how HRQOL findings have contributed to a better understanding of the overall treatment effectiveness of new drugs[7-9]. For example, one may assess the time to HRQOL deterioration[10-15], which allows comparison of treatments in terms of median HRQOL deterioration-free survival. More rarely, also the time to temporary or sustained HRQOL improvement has been assessed as a possible outcome in cancer[16-18].

However, the development of modern anticancer therapies, such as targeted therapies (e.g., small-molecule drugs) or immunotherapies (e.g., immune checkpoint inhibitors), is rapidly changing the cancer landscape by improving prognosis for several cancer populations, making HRQOL improvements a more and more frequent possibility[17,19-22]. Notably, these therapies have been shown to improve HRQOL outcomes across various disease settings, including both those with relatively healthy and newly diagnosed cancer populations[23] and those with highly debilitated conditions and more advanced disease[19,24]. To illustrate, a recent phase II trial including children and young adults with relapsed/refractory acute leukemia (i.e., a potentially life-threatening condition), treated with an innovative immunotherapy approach, found progressive HRQOL improvements across various health domains, from treatment start up to 12-months of observation[24].

In this work, our first objective is to propose *time to HRQOL improvement* (TTI) and *time to sustained HRQOL improvement* (TTSI) as outcomes of growing importance in cancer research[25]. TTSI reflects

the hypothesis that the improvement in HRQOL may last over a pre-specified time period, paralleling the clinical concept of sustained response of a treatment.

A secondary objective is to introduce the competing risks approach for both TTI and TTSI analyses, proposing definitions, estimation methods and reporting procedures.

2. Theoretical framework and definitions

2.1 Event of interest

The event of interest is the improvement in patients' self-reported HRQOL, which is typically assessed by questionnaires frequently comprising different scales, each representing a specific HRQOL domain. We define the event "HRQOL improvement" as the first clinically meaningful improvement occurring in a given scale or in at least one among different scales[26] (e.g. a cluster of symptoms), depending on the research question.

In order to deem an improvement in a given HRQOL scale as clinically meaningful, we need to define a minimal important difference (MID), i.e. a threshold identifying the smallest change in the score of the scale which is perceived as important by the patient[27] . In this work, we will use the individual-based MID of 5-points for each scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)[28], as proposed in previous work[29] and frequently used in cancer research using this questionnaire.

2.2 Time origin

Another relevant issue to define TTI analysis is the origin of the time period to be measured. The HRQOL score at the initial time point will be referred to as the "reference" score. Typically, the reference is set as the baseline (pre-treatment) score, but it might also be defined differently[26] depending on the study design. For example, a cancer patient might report a HRQOL improvement between the first post-treatment and the pre-treatment assessments. Indeed, this might reflect the patients' transition from being diagnosed to benefit from earlier effects of treatment, without experiencing possible long-term treatment-related side effects. Therefore, measuring TTI from the first post-treatment score would likely rule out this effect, providing a measure of HRQOL improvement already including the effects of patients' coping, both with the disease and the treatment schedule.

2.3 Time to HRQOL improvement and time to sustained HRQOL improvement

We define TTI as the "time to the first HRQOL evaluation showing an improvement at least equal to the stated MID, with respect to a reference HRQOL score" (see Appendix A). We define a "sustained" HRQOL improvement as the first improvement *not* followed by any further deterioration on the same scale above the MID, with respect to the reference score (see Appendix A).

3. Estimation strategy

So far, the Kaplan-Meier (KM) curves and Cox proportional hazards (PH) model have been typically used to estimate both TTI and TTSI[16,17]. However, these methods cannot incorporate the possible

impact of previous occurrence of other events, on the chance of a HRQOL improvement to occur at a given time-point. For example, if we define the event of interest as the first improvement in one of at least two HRQOL scales, the earlier improvement in one of these scales would rule out the HRQOL improvement coming first in the other scale(s). In addition, the previous occurrence of worse clinical outcomes (e.g. toxicity, relapse, disease progression or death) would preclude the HRQOL improvement coming first. Using KM and Cox PH methods would likely cause a bias in the estimate of the incidence function of improvements in either scales. Indeed, when assessing TTI and TTSI we should be able to account for possible competing events, using the Fine-Gray model[30].

The first quantity we are interested in is the *cumulative incidence* of the earliest HRQOL improvement (EQI) over the follow-up period, which we will estimate using the cumulative incidence function (CIF)[30] (see Appendix A). The second quantity we want to estimate is the sub-distribution hazard (SDH), to assess the possible impact of one or more covariates on the cumulative incidence of EQI (see Appendix A). For example, the SDH could be used to estimate the rate of the EQI of one group vs another as the coefficient of a binary pre-treatment variable, with Gray's test[31] to assess its statistical significance. More details about CIF and SDH can be found in Putter et al.[32] and Austin et al.[33]

In case of intermittent missing values in a HRQOL scale, we will use the last previous score available as a proxy for calculations[26], after having checked the type missing data generating mechanism. Those individuals neither experiencing a HRQOL improvement nor a competing event will be censored at their last follow-up. A specific issue to consider in TTI/TTSI analysis is the possible presence, for any HRQOL scale, of patients who have a null chance of improvement from the reference score. This depends both on the type of measure and the MID threshold. For example, an individual with a reference score differing less than the MID from 0 on the EORTC QLQ-C30 fatigue scale will not be able to experience an improvement at any subsequent time point. Such patients should be included in rather than excluded from the analysis, taking into account that they are not at risk for the occurrence of

the event of interest. However, if simply included in a Cox PH model, these individuals would actually be considered at risk for the occurrence of the event of interest, which we know is not true. Therefore, we will consider these patients as having experienced a competing event at the reference time point.

4. Data and methods

The case study we used in this work comprised 124 newly diagnosed patients with Chronic Myeloid Leukemia (CML), undergoing first line therapy with nilotinib (i.e., a second-generation tyrosine kinase inhibitor). At study entry, the median age of patients was 49.5 years (range 18-81), 64.5% (n=80) were male and 60% (n=74) had at least one comorbidity. Further details about pre-treatment patients' characteristics are shown in Table 1. These patients were enrolled in a single-arm study (phase 3b), to evaluate the efficacy of nilotinib 300 mg twice daily, measured in terms of overall, progression-free and event-free survival[34] . As part of this study, HRQOL was measured at baseline (before treatment start), then at 3, 6, 12, 18 and 24 months, by the EORTC QLQ-C30 questionnaire[28]. HRQOL compliance (i.e. the number of questionnaires assessed out of those expected) was XX% (), XX% (),XX% (), XX% () and XX% (), respectively at 3, 6, 12, 18 and 24 months. Investigation of missing data generating mechanism suggested these were neither MNAR nor MAR , supporting the use of (i.e. last observation carried forward (LOCF) imputation method.

[INSERT TABLE 1 HERE]

4.1 Statistical analysis

For the purpose of illustration in this work, we focused on the earlier time to improvement either in fatigue (FA) or physical functioning (PF) as the primary scales to be analyzed. As the PF scale can

reflect, among other things, self-reported limitations in activities that might be related to the burden of fatigue, the individual patterns over time of FA and PF are likely to be correlated. For example, in the current data the baseline scores of these scales show a high correlation (ρ= -0.77). Based on this, when assessing the timing of possible earliest improvements on each of these scales (e.g. FA), we simultaneously accounted for possible earlier occurrence of either improvements in the other scale (e.g. PF),disease progression, treatment failure, or suboptimal response or toxicity as a competing event. In addition, we assessed the time to improvement in all the remaining symptoms scales of the EORTC QLQ-C30 questionnaire, i.e. nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation and diarrhea. As we considered these as secondary scales, we assessed the time to improvement for each of these independently of one another. In these analyses, we also considered as a competing eventthe possible earlier occurrence of either disease progression, treatment failure, suboptimal response or toxicity.

In addition, we also ran the analyses without considering these clinical competing events, to assess the sensitivity of TTI and TTSI to their occurrence.

We performed the same analyses described above also considering the first post-treatment HRQOL score (i.e. at 3rd-month assessment) as the reference score and a sustained HRQOL improvement as the event.

For illustrative purposes, we also assessed the possible impact of different pre-treatment variables on TTSI from baseline on the fatigue scale, by estimating the corresponding SDH. These variables were comorbidity (Yes vs No), Sokal risk (Low vs higher) and hemoglobin level (<10 mg/L vs ≥10 mg/L).

All analyses were performed by using R software v. 3.5.2 and code is available in Appendix B.

5. Results

5.1 Baseline reference score

5.1.1 Time to HRQOL improvement

The CIF of FA was consistently equal to or higher than that of PF, throughout the entire follow up period (figure 1A). Also, the time to achieve the same proportion of events was increasingly shorter for FA than for PF. For example, it required 3.2 vs 3.5 months to observe 20% (n=25/124) of patients experiencing an earlier improvement in the FA and PF scales, respectively. However, 30% of improvements were observed at 3.5 months for FA vs 6.7 months for PF. Overall 48% (n=60/124) of patients experienced an earlier improvement in FA vs 35% improving first in PF and the majority of improvements occurred within the first six months for both scales, (80%, n=48/60, in FA and 76.7%, n=33/43, in PF). When not considering clinical competing events, the time to reach 20% of PF improvements was reduced from 3.5 to 3.3 months, while FA improvement remained the same (i.e. 3.2 months).

With respect to other symptom scales (Table 2), those with the highest overall cumulative incidence were pain (34.7%, n=43/124), followed by insomnia (31.5%, n=39) and constipation (27.4%, n=34).

[INSERT FIGURE 1 HERE]

5.1.2 Time to sustained HRQOL improvement

Overall, there were 42 and 31 sustained earlier improvements in FA and PF, the majority being within the first six months, 71.4% (n=30/42), and 67.7% (n=21/31) for FA and PF, respectively. The cumulative incidence of FA was equal to or higher than that of PF (figure 1B). The time to achieve 20% of sustained improvements earlier than in the competing scale was 3.5 months for FA vs 11.8 months for PF. Without clinical competing events, the time to reach the same proportion of sustained improvements was slightly lower (3.3 months) for FA and remarkably lower (3.8 months) for PF.

Pain, insomnia and appetite loss were the top three remaining symptom scales showing the largest proportion of sustained improvements, 25.8%(n=32/124), 25.8% and 22.6% (n=28/124), respectively (Table 2).

[INSERT TABLE 2 HERE]

5.2 First post-treatment reference score

5.2.1 Time to HRQOL improvement

When considering the third month HRQOL assessment as the time origin, the cumulative incidence of FA was higher than that of PF (figure 2A). Overall, 33.1% patients (n=41/124) experienced an improvement in FA earlier than in PF, while 25.8% (n=32/124) improved first in PF. The time to reach 20% events was 6.7 vs 11.8 months respectively for FA and PF, respectively. The time to reach the same proportion of improvements without considering clinical competing events decreased to 6.5 months for FA and 6.9 months for PF. Among the secondary scales (Table 2), pain was the symptom most frequently improved (27.4%, n=34/124), followed by nausea and vomiting (22.6%, n=28/124) and insomnia (21.8%, n=27/124).

5.2.2 Time to sustained HRQOL improvement

The differences between FA and PF curves were negligible (figure 2B). The overall proportion of sustained improvements was similar for both scales 17.7% (n=22/124) and 16.9% (n=21/124) for FA and PF, respectively. For the secondary HRQOL scales (Table 2), the top three symptoms showing most frequently a sustained improvement were pain (22.6%, n=28/124), nausea and vomiting (19.4%, n=24/124) and insomnia (18.6%, n=23/124).

[INSERT FIGURE 2 HERE]

5.3 Baseline variables and time to sustained improvement in fatigue

A lower baseline hemoglobin level was associated with a higher likelihood of experiencing an earlier sustained improvement in FA (HR = 2.12, 95% CI = 1.09 to 4.12, $p = 0.027$). The CIFs are displayed in Figure 3. None of the other baseline variables investigated were found to be prognostic for a sustained improvement in fatigue.

[INSERT FIGURE 3 HERE]

6. Discussion

We have proposed the time to HRQOL improvement (TTI) and the time to sustained HRQOL improvement (TTSI) as potentially important outcomes of interest in cancer clinical research with modern anticancer therapies. We have described the clinical rationale and the methodological framework for both outcomes, suggesting definitions and procedures for analysis and reporting.

We proposed reporting TTI and TTSI findings as cumulative incidence curves. Indeed, a HRQOL improvement is a positive event for a patient and the interpretation of results is more straightforward if reported as a cumulative occurrence over time, rather than as an "improvement-free" survival. Additional specific recommendations for reporting about time to HRQOL improvement analysis are to clearly state the scale(s) to be investigated and defined as primary endpoints, the event of interest and possible competing event(s), the MIDs as well as the reference score and the type of assessed HRQOL improvement (whether sustained or not). In addition, for both TTI and TTSI the general

recommendations for reporting about HRQOL studies still hold (e.g. multiple testing, missing data and imputation methods, sensitivity analyses).

We described and recommended the use of the Fine-Gray model, as it allows to take possible competing events into account, such as death, as well as to correctly include in the analyses also those patients who are not at risk of improvement.

Taking into account competing risks when estimating TTI and TTSI allows to directly address the occurrence of intercurrent events as defined in the estimands framework published by ICH[35], which indeed "complicate the description and interpretation of treatment effects" [35]. With respect to intermittent missing HRQOL measurements, in this work we used last previous score available as a proxy for calculations[26]. We highlight that the choice of the imputation method needs to be supported by the investigation of the missing data generating mechanism, and that different imputation methods are available.

We would like to note that the concerns about competing events and the corresponding modeling approaches could be a general issue in the analysis of PROs, e.g. applying also to the time to HRQOL deterioration analysis. For example, Fatigue and Physical functioning scales are highly correlated and likely share a number of prognostic factors. This link between the event of interest and the competing event could bias incidence curves and predictors for HRQOL improvement. We therefore advise to assess the robustness of findings by sensitivity analyses, using e.g the inverse probability of censoring weighting (IPCW) method.

We note that TTI and TTSI have lower statistical power than those analyses relying on the original metric or ordinal scores, as both are based on dichotomized scores. This issue should be considered when designing a study considering either TTI or TTSI[36], as well as issues related to multiple testing and inflation of type I error, when considering more scales as primary endpoints Furthermore, there are

different available definitions of MIDs[37-39] . While statistics such as hazard ratios from comparative analyses may be fairly robust towards variation in MIDs, the actual time to improvement might vary substantially. Indeed, MID thresholds are known to differ across patient populations and with respect to the smallest detectable change for a specific PRO measure. This could limit the comparability between studies using different MIDs, making meta-analysis difficult. Therefore, the MID should be carefully chosen for each study and sensitivity analyses could be planned, using different MIDs to assess the robustness of results[35].

Indeed, TTI and TTSI have also powerful characteristics, e.g. they can consider the within-subject time sequence of improvements in different possibly correlated HRQOL aspects. In addition, both are based on the proportion of clinically significant improvements in individuals, rather than on clinically significant improvements in average HRQOL group scores, better reflecting the "patient-based" definition of clinical significance. Furthermore, TTI and TTSI provide additional relevant information about the speed with which HRQOL improvements occur, in addition to simply reporting the improvement proportions at different time points.

Our work has limitations. First, we did not investigate the possibility of defining other events as a HRQOL improvement, such as "full remission". In addition, we did not explore the possibility of improvement in some scales and deterioration in others for the same patient, as well as the improvement for some patients and deterioration for others in the same scale. However, we are currently working to assess these issues in further research. A third limitation is that we used only one of different available MID thresholds, which is not scale-specific. However, we chose the 5-points MID for illustration purposes and the possible use of other MIDs for TTI/TTSI analysis is straightforward.

Our work also has notable strengths. First, we used empirical data from a real-life study in a relevant clinical setting. In addition, we provided a robust clinical rationale supporting the analysis of TTI and TTSI. Third, the analytic approach we proposed relies on a well-established statistical framework, which clinicians are familiar with and can be straightforward set up in applied research. Fourth, we described how the Fine-Gray model can be used to analyze the earlier improvement in competing HRQOL scales and to include those patients with not improvable scores in the analysis.

The use of TTI and TTSI can be of interest in addressing a number of clinically relevant research questions. For example, it can be used to compare different treatments with similar survival outcomes, favoring that with the highest cumulative probability for HRQOL improvement at a fixed time point or that with the shortest time to reach a predetermined proportion (e.g. 50%) of improvements. One could also investigate the possible prognostic impact of baseline (i.e., pretreatment) variables (e.g., a symptom score or a risk-index category) on the time to HRQOL improvement. Another possible research question might be to identify, in a cluster of symptoms, that symptom reaching the earliest clinically important improvement.

In conclusion, both TTI and TTSI can be used in various clinical research settings and with different cancer types, especially in those cases where different anticancer therapies are available with similar clinical outcomes. Considering the increasing trend towards the use of targeted therapies or immunotherapies and the resulting increase in survival outcomes for many patients, we envisage the time to temporary or sustained HRQOL improvement as important outcomes of interest to be assessed in future HRQOL studies in oncology.

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Authors' contributions

Conception and design: FC, FE

Data analysis and interpretation: All Authors

Statistical analysis: FC, GSC, AA, KS, JMK, KVS, EC

Manuscript writing: All Authors

Final approval of manuscript: All Authors

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