Author’s response to reviews

Title: Health-related quality of life as an endpoint in oncology phase I trials: a systematic review

Authors:
Frédéric Fiteni (fredericfiteni@gmail.com)
Isabelle Le Ray (isabelle.le.ray@normalesup.org)
Ahmad Ousmen (aousmen@chu-besancon.fr)
Nicolas Isambert (NIsambert@cgfl.fr)
Amélie Anota (aanota@chu-besancon.fr)
Franck Bonnetain (franck.bonnetain@univ-fcomte.fr)

Version: 2 Date: 14 Feb 2019

Author’s response to reviews:

Responses to the Editors and Reviewers

We thank the editors for giving us the opportunity to respond to the reviewers’ comments and suggestions, which allowed us to improve the quality of our manuscript.

All remarks and recommendations made by the editors and reviewers have been taken into account and the manuscript was modified accordingly.

Point-by-point responses to the comments and suggestions are provided below.

Everardo Saad (Reviewer 1):

In this manuscript, authors report the results of a systematic review of the literature pertaining to the assessment of health-related quality of life (HRQOL) in phase I trials in solid tumors among adult patients. Not surprisingly, HRQOL has been reportedly used very rarely. I personally do not see this as a problem and do not believe HRQOL assessment really adds value to phase I trials. Most phase I trials assess patients for a short period of time and at doses below the MTD or RP2D, thus providing little role for HRQOL assessment. Despite my personal views, I believe the manuscript has merit and is well written. A discretionary point is the fact that reference 7 does not correspond to the citation to Paoletti’s work in the text. More importantly, unless I missed it, the authors have not pointed to limitations of their work. They could perhaps say explicitly why hematological malignancies were left aside, and how they have dealt with papers that included patients with both solid tumors and hematological malignancies. Arguably, the
period of analysis is short, so authors could build the case for why they chose to restrict the period.

Thank you for these remarks

We have deliberately chosen to review articles from 2012 to be representative of the current use of HRQoL in phase I trial. This point was specified in the manuscript: “Literature search was performed from 2012 to be representative of the current use of HRQoL in phase I trials. We focused on studies in adults solid tumors. Therefore, haematological and pediatric phase I were excluded.

The reference corresponding to Paoletti’s work has been added.

A paragraph on limitations of our work has been added: “The main limitation of our study is the short number of studies with HRQoL as endpoints. Three papers had HRQoL as primary endpoint but none of them identified the RP2D with HRQoL as endpoint. Therefore, we are unable to provide any example of a drug that is used in the daily life and which dose has been determined by HRQoL or PROs in phase I. Moreover, the side-effects of the drugs are frequently not known as many drugs assessed in phase I are first-in-human and can be first-in-kind. Therefore, the choice of a HRQoL instruments can be difficult in this context.”

Galina Velikova (Reviewer 2): This article presents a systematic review of phase I trials that have incorporated quality of life as an endpoint.

Major comments

In the background section the authors have made a good justification why quality of life might be helpful in Phase I trials. The authors state that quality of life questionnaires can capture moderate toxicity experienced over a long period of time. However, they could provide further elaboration on the fact that in Early Phase trials, the methodology is very strict and regulated. Often the side-effects of the drugs are not known and therefore it is difficult to choose a quality of life instrument. It could be argued that further evidence is needed on the usefulness of quality of life instruments in Early Phase trials before they are recommended.
Thank you for this remark.

We added in the discussion section “Moreover, the side-effects of the drugs are frequently not known as many drugs assessed in phase I are first-in-human and can be first-in-kind”. Therefore, the choice of a HRQoL instruments can be difficult in this context.

Line 91 - the authors should justify the statement that "doses recommended based on current MTD definition are higher than needed” and add a reference.

Thank you for this remark.

We modified this sentence to temper our statement and added a reference: “doses recommended based on current MTD definition could be higher than needed especially for molecularly targeted agents ” and added a reference.

Line 104 - the objective of this study is stated as to assess the current use of health-related quality of life as an endpoint in Phase I trials. The authors should be more specific here and state that this covers both primary and secondary endpoints as per their subsequent search strategy. Furthermore, it may be useful to specify what their hypothesis was. Did they expect to see many Phase I trials with health-related quality of life endpoints or not.

Thank you for this remark.

We added in introduction “However, its use is most likely not widely spread, as a primary or secondary endpoint.”

We added in “Search strategy and Selection for studies”: “Eligible trials were phase I trials in oncology with HRQoL as endpoint (primary or secondary).”

The results are perhaps not surprising. Interestingly two trials had quality of life as a primary endpoint. The majority (60%) had MTD as the primary endpoint as perhaps expected. This is a relatively small systematic review. It will be helpful for the reviewers to provide more information on the two trials that included health-related quality of life as a primary endpoint but then didn't use it subsequently to determine MTD subsequently. Why did they not use it and what other measure did they employ instead?
Thank you for this remark with helped us to reanalyze these two studies: Ringash et al. and Rouanne et al.

The study of Rouanne et al. was an ancillary study which aimed to assess sexual quality of life that’s why we don’t think it can be considered as a primary endpoint.

The study of Ringash et al. was a separate publication of the QoL endpoint. The primary endpoint was actually “incidence of radiation-induced acute grade 4 toxicity” and published in a separate paper. We modified our article accordingly.

Therefore, no study used QoL as primary endpoint or determined the RP2D with QoL.

We modified our article accordingly.

We added in the discussion section comments on studies which compared QoL between the different dose levels: “None of the studies included in our review used HRQoL as primary endpoint or identified the RP2D using HRQoL measurement. Three studies analyzed HRQoL according to the dose levels. In the Ringash et al. and Tsubata et al. studies there was no relationship between dose level and HRQoL while they observed increased toxicity according to the dose of treatment. In Anota et al. study, patients presented a longer TTD at the MTD (10 mg idarubicin) than at the lower level (5 mg idarubicin) for global health status, physical functioning, fatigue and pain dimensions. These results consolidate the selection of the RP2D.”

In table 2, I would like to see more information on whether, in any of the listed studies with the statistical methods employed, the information was useful and influenced any decisions or subsequent Phase II trials. In the two trials that had quality of life as primary endpoint, how was MTD determined? Did quality of life results help in any of these trials?

Thank you for this comment.

We added a column in the table 2 on “HRQoL data interpretation”.

As mentioned above we added comments on studies which compared QoL between the different dose levels.
In the discussions, the authors seem to suggest from line 201 onwards that NCI PRO CTCAE should be added to the current reporting using CTCAE to define MTD. It appears that they argue that in addition to NCI PRO CTCAE, health-related quality of life should be measured to determine the impact of the toxicities on patients’ lives. This point could be expressed more clearly and strongly.

We modified the discussion to clearly explain the idea that HRQoL questionnaires could be a complement to toxicities: “HRQoL questionnaires could bring an added value in phase I as a complement to results obtained on toxicity, as the study of Anota et al. to see if there’s no impact on HRQoL at the MTD compared to lower doses. A longitudinal analysis of HRQoL could be an alternative way to assess the impact of the MTD in a clinically meaningful way.”

The general impression of this article is that it doesn’t bring much additional information to what an oncologist would expect. It will be useful if the authors could express their opinion whether in any of these trials health-related quality of life contributed and how it was interpreted to make the case for its future inclusion more routinely. Even one example where it has changed the decision-making would be extremely helpful. This could lead to some more specific suggestions as to how this field could be moved forward. At present, the article does not provide good direction for the future apart from the recommendation for more methodological research.

Thank you for this comment.

We strongly think that HRQoL and/or PRO measurements could bring an added value in phase I in two ways:

- either: PRO-CTCAEs scale could be a complement or used rather than the NCI-CTCAEs scale to determine the RP2D in a more patient-oriented perspective.

- or we could use HRQoL questionnaires as a complement to results obtained on toxicity, as the study of Anota et al. to see if there’s no impact on HRQoL at the MTD compared to lower doses

We modified the discussion to better explain this ideas: “we could use the PRO-CTCAEs scale rather than the NCI-CTCAEs scale to determine the RP2D in a more patient-oriented perspective. Nevertheless, some moderate adverse events which could have an impact on patients’ HRQoL over time might not be taken into account by the PRO-CTCAE. Further researches are mandatory and the first step could be to implement PRO-CTCAEs as secondary endpoint in order to compare the results obtained with the NCI-CTCAEs.

HRQoL questionnaires could bring an added value in phase I as a complement to results obtained on toxicity, as the study of Anota et al. to see if there’s no impact on HRQoL at the
MTD compared to lower doses. A longitudinal analysis of HRQoL could be an alternative way to assess the impact of the MTD in a clinically meaningful way.”

We hope that our revised manuscript will satisfy the Editorial Board of the journal and that the paper will be found suitable for publication.

We stand ready to respond to any queries that may arise.

Sincerely,

Frédéric Fiteni