Author's response to reviews

Title: The Association of Quality of Life with Potentially Remediable Disruptions of Circadian Sleep/Activity Rhythms in Patients with Advanced Lung Cancer

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Please find enclosed the revised manuscript MS: 1834286941369072 - The Association of Quality of Life with Potentially Remediable Disruptions of Circadian Sleep/Activity Rhythms in Patients with Advanced Lung Cancer

My colleagues and I found the reviewers’ insights, comments, and criticisms very informative, occasionally very challenging to cope with, and on occasion contradictory.

Dr. Rich made three points but basically, he wondered whether patients who failed prior chemotherapy had sufficient time to recover from treatment induced symptoms before participating in our trial.

Consequently, we addressed his first comment by adding to the abstract the addition of this sentence

“Fifty three patients were starting their definitive therapy following diagnosis and thirty one patients were beginning 2\textsuperscript{nd} line therapy. Among the patients who failed prior therapy, the median time between the completing definitive therapy and baseline actigraphy was 4.3 months, (interquartile range 2.1 to 9.8 months).”

We addressed his third point by adding the following to the end of patient characteristics section of the results,

“The median time between terminating first line therapy and the administration of actigraphy in the ten outpatients was 51.6 months (range 7.9 to 78 months), but for in patients it was 3.5 months (0.8 to 33.5 months).“

This data addresses Dr. Rich’s concern about that a significant fraction of patients participating in this trial had insufficient time to recover from the effects of prior cycles of chemotherapy.

Dr. Rich point 2; is addressed with the addition of the phrase “treatment cycle for this trial” in the first sentence in the section protocol summary (pg7) in results.
Dr. Waterhouse made numerous suggestions on how to improve the introduction. For example, we followed his suggestion to rephrase “circadian organization” in the last paragraph in the introduction with ‘activity intensity and timing’ to reflect what wrist actigraphs actually measure.

Methods

Dr. Waterhouse suggested that we provide more details about our analysis and challenged us to justify the use of cosinor analysis for this investigation. We provide an expanded explanation of the details of the actigraph parameters in appendix 1. Furthermore, we use the outputs of cosinor analysis to produce the indices that used by the investigators in references 14 and 20. Also in appendix 1 we provide the details about our autocorrelation analysis that is used to demonstrate the validity of using cosinor analysis for evaluate these patients circadian rhythm.

We followed Dr. Waterhouse’s suggestion to improve the intelligibility of the last sentence in the methods.

Results

We have revised all of the tables in light of Drs. Waterhouse and Chen’s comments.

Pg 13.

Following Dr. Waterhouse’s advice we have improved the positioning of our legends.

Dr. Waterhouse observed that the Results section is littered with statistical results. He hinted that this made the results a rather hard read and he suggested that we try to create a summary table of our main results. We developed Table 6 to address this observation.
Dr Chen was the most challenging reviewer. Unlike the others, he found the manuscript a difficult read;

1. Appendix 1 addresses Dr. Chen and Waterhouse concern that the text had too dense with statistical and circadian jargon.
2. We removed significant from page 11 line 18.
3. Hopefully, oncologists will be a receptive audience for this data. Almost to the doc, oncologists who treat lung cancer patients will think that COPD is a confounding variable for any investigation of circadian organization. We think this tiny section should remain.
4. The section on the relationship with QoL and other prognostic variables is interesting in itself, but as Dr. Chen pointed it not directly relevant to the paper, so it was removed.
5. We have revised all of the tables to reflect Drs Chen and Waterhouse’s comments and I have added a large table to collate all of the statistically significant correlations between QoL parameters and sleep parameters for outpatients in table 6.
6. Dr Chen is a very careful reader, in our discussion we focused on the finding that outpatients did not report insomnia as a problem, however, inpatients did. Hospital routines seem to be designed to suddenly increase the number of untoward awakenings at night, consequently, we can hypothesize that these patients feel sleepier than they did a week ago, while outpatients have become adapted to their progressive sleep fragmentation. So we have inserted the following in the
   a. Discussion “An interesting finding was the lack of a significant relationship between a self-reported insomnia among outpatients and any objectively measured actigraphy parameter. This finding is surprising considering that actigraphy data showed that virtually every patient’s sleep was fragmented and unconsolidated and these patients self report of their sleep quality, as measured by a validated sleep questionnaire, was indistinguishable from insomniacs. This non sequitur between universal objective signs of very poor sleep and the perception of insomnia among advanced lung cancer is interesting. It seems as though, in cancer patients as in the healthy elderly, the perception of nocturnal sleeplessness and the reality of it are at odds. Inpatients did report an association between an actigraphy parameter and insomnia, we can speculate that hospital routines involve a sudden increase in number of untoward nighttime awakenings that results in the patients feeling much sleepier than they did in the prior week.”
7. Overall there is not much data linking parameters measuring circadian activity with QoL data. However, Berger et al and Bogdan et al provide interesting results which appear to be consistent with ours. Bogdan failed to find a relationship between a self report of insomnia and parameters of circadian rhythms and Berger reported that breast cancer patients’ circadian activity differs from controls. Both
references and comments on their work were inserted in the appropriate sections of the discussion.

8. I am reluctant to discuss Dr. Chen’s idea of response shift in this discussion. However, we are evaluating the effects of tumor response or lack of response, and the administration of melatonin on patients in a subsequent paper. We will have data that will directly address issues of response shift and I would prefer to discuss that issue with some data in hand.

We are looking forward to review of our revised manuscript and if there are further issues and thoughts from the reviewers I promise a much quicker response.

Best Wishes

Jim Grutsch