Reviewer’s report

Title: Prevention of Acute Radiation-Induced Proctitis by Aloe vera: a Prospective Randomized, Double-blind, Placebo Controlled Clinical Trial in Pelvic Cancer Patients

Version: 1 Date: 20 Nov 2019

Reviewer: Ferran Torres

Reviewer's report:

The merits of conducting a clinical trial in this scenario are recognized and this initiative is endorsed. However, there is a number of points which should be addressed/clarified before a positive recommendation for acceptance can be issued. Please, answer and discuss, as appropriate, the point-by-point review attached below.

MAJOR COMMENTS

1. Comment on the exploratory nature of this study. While valuable information may be gathered from exploratory studies, they should be identified so. There are a number of issues that suggest that this trial should be classified so: the limited sample size, the number of endpoints implicated without a clear definition of their priority and the lack a single endpoint predefined and the number of time points without a predefinition of the priority of the assessment.

Material and methods

2. In the study design, it is stated: "Patients were allocated to the study group according to Random Number Table.". It appears that investigators were not concealed on the treatment assignation and this would be a violation of the randomisation rule. However in the Calculation of the number of patients and randomization subsection it is stated that "Patients, treatment team, and the investigator of clinical responses did not know the types of interventions. At the end of the study, the principal investigator decoded the numbers of consumed ointments and assigned each to the appropriate group correctly." Please discuss.

3. Main and Secondary outcomes. Unclear which is/are the main endpoint/s.

The primary endpoint should be clearly defined in the endpoint section. Ideally, it should be the incidence of proctitis in both arms of treatment at the end of 6 weeks (please define proctitis). Which is in accordance with the sample size calculation.

If the total score of the 4 components is the main outcome, please state so. If it was not predefined and it is a post-hoc, please define so. Also, define whether the total score is a sum or a mean (I assume mean) of the components.
In case that a main outcome was not predefined, there might be multiplicity issues associated with the trial design and interpretation, please include a comment in discussion.

All the secondary endpoints should be defined one by one in this section. Add also when, how and the measurement units of them.

Please, arrange tables in concordance with the final review of the outcomes, so that there is a clear distinction on the endpoint priority.

4. Sample size issue. In the subsection on the calculation of the number of patients and randomization section it is stated: "Because of the high incidence of acute radiation proctitis symptoms up to 75% patients1,2, we calculated that for a power of 0.8, significance level of 0.05, and an allowance of 10% lost to follow-up rate, for detecting a decrease in ARP symptoms by one-half, 40 patients would be enough."

First, this is not traceable, for binary outcomes it would be needed also the control rate to calculate the sample size. Secondly, the sample size is normally calculated for the primary endpoint, but this is unclear in this case, presentation of the results is based on the score (not in the incidence) and there is no justification on this point.

5. Inferential tests and descriptive results. There is an inconsistency between the inferential analysis with the Mann-Whitney non-parametric test and the reporting of "Mean± SD (Standard Deviation)". This is not understood. If the results do not follow a Gaussian distribution, mean and SD should be replaced by median [Percentile 25th - 75th]

6. Please describe the use of the logistic regression in the methods section.

Please note that "hazard ratios" are not the appropriate risk estimates from this analysis (see section Effect of Aloe vera rectal ointment on symptoms"
Have you used an ordinal logistic regression analysis? Otherwise, if you have dichotomised the symptoms score please state and describe it in the methods section.

7. Handling of missing data is not reported

Results

8. The results of the primary endpoint should be clearly identified.
The incidence of proctitis for every arm should be reported in a prominent position of the results with the 95%.

9. Table 1. P-values for baseline characteristics in a randomised setting are inappropriate. Please delete them.

10. Tables 2-3 and figures 2-3 should be re-assessed.

First, they should be unified because of clear redundancies. Sample sizes per arm and time should be reported somehow; if there were not missing data this could be addressed by a footnote. P-values are not understood, do they refer to the last time measurement (supposed to be the main time-point?, although unclear).

I suggest to use a unique results table including the incidence, the baseline and the last measurement timepoint for clinical presentation and symptoms, with the p-value for week 6 between arm comparisons. The odds ratio should be included in the same table. Figures may be maintained showing the complete time evolution but please priories the order according to the discussion on the endpoint priority and include variability in the plots. If 95%CI are too wide (given the small sample sizes) include then the standard error of mean.

Please include appropriate figure legends and footnotes so that they are sufficiently explicit. The same for all tables, please include everything that is not direct interpretation in footnotes, for instance the use of Mean±SD (or median [Percentile 25th - 75th]) or abbreviations.

11. Results CRP are only shown partially, with only a p-value: "Quantitative measurement of C-reactive protein (CRP) showed no significant difference between groups (p=0.33), but still favored Aloe group."

Please report descriptive results for this variable, for instance mean±SD per group or median [Percentile 25th - 75th]

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

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