Author's response to reviews

Title: A phase II study of cisplatin with intravenous and oral vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy with oral vinorelbine and cisplatin for locally advanced non-small cell lung cancer

Authors:

Delphine Lerouge (D.LEROUGE@baclesse.fr)
Alain Rivière (A.RIVIERE@baclesse.fr)
Eric Dansin (e-Dansin@o-lambret.fr)
Christos Chouaid (christos.chouaid@sat.aphp.fr)
Cécile Dujon (CDujon@ch-versailles.fr)
Roland Schott (r.schott@strasbourg.fnclcc.fr)
Armelle Lavolé (armelle.lavole@tnn.aphp.fr)
Vincent Le Pennec (lepennc-v@chu-caen.fr)
Elizabeth Fabre (Elisabeth.FABRE-GUILLEVIN@hop.egp.ap-hop-paris.fr)
Jacky Crequit (jacky.crequit@ch-creil.fr)
Francis Martin (f.martin@ch-compiegne.fr)
Stéphanie Dehette (s.dehette@ch-compiegne.fr)
Pierre Fournel (Pierre.FOURNEL@icloire.fr)
Eric Lartigau (e-lartigau@o-lambret.fr)
Gérard Zalcman (gerard.zalcman@yahoo.fr)

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E-mail: d.lerouge@baclesse.fr
        zalcman-g@chu-caen.fr

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Reviewer 1: Hidehito Horinouchi

Authors reported a phase II trial examined sequential chemoradiotherapy using cisplatin and vinorelbine. There were several important and minor problems in the manuscript.

Major comments:

1) As authors referred, there were several trials which showed superiority of concurrent chemoradiotherapy over sequential chemoradiotherapy. It should be mentioned as an important limitation of this trial.

We thank Reviewer 1 to re-assess, (but we thought it was clear in the material & methods section), that the goal of our trial was not to compare sequential versus concurrent chemoradiotherapy, but to explore the administration of oral vinorelbine in the concurrent phase to study the feasibility of this way of vinorelbine administration, as compared to IV infusion, in terms of tolerance, but also efficacy.

In fact, we mentioned in our introduction section that trials addressing radio-chemotherapy, actually showed superiority of the association, either concurrent or sequential, over radiotherapy alone. Our trial was not questioning the sequence or the concurrency of the association, but was a rather pragmatic trial, since in real daily life, it is difficult in most of the cases, at least in France, to begin radiotherapy as soon as the first cycle of chemotherapy.

Anyway, we feel that our results show that beginning by chemo alone, followed by a concurrent chemo-radiotherapy sequence, does not represent an “important limitation”, since they are in perfect range with the results of most large concurrent radio-chemotherapy trials published to date.

Moreover, if two cycles of induction chemotherapy, followed by concurrent chemo-radiotherapy (our design) failed to improve significantly survival as compared with front-line concurrent chemo-radiotherapy, this sequence was not inferior (14 months

Finally, Dr. Van Houtte (Van Houtte P et al., abstr. P2.24-021) presented at last WCLC meeting in Sidney, a meta-analysis of 5 randomized trials (534 patients) on individual data, comparing induction versus consolidation chemotherapy associated to concurrent radio-chemotherapy: no difference in terms of PFS or OS was found with a median OS of less than 18 months strictly identical to our findings in the current trial…with an oral drug.

As Reviewer 1 could have been mislead by the way our introduction was structured, we slightly transformed this section and we re-structured our Discussion section, to put in better perspective the aim of our study, i.e. to explore the oral formulation of vinorelbine as a bona fide way of administration during concurrent chemo-radiotherapy phase of the treatment.

2) Authors should clarify whether the trial met the primary endpoint or not. ORR was lower than expected in the pre-planned statistical consideration,

Again, we thank the reviewer for underlining a possible ambiguity in the way we reported the results of this trial.

As mentioned in the material and methods section, this was a phase 2 trial of which primary endpoint was overall response rate (ORR).

A very classical Fleming design, was used with a 90% power and an alpha risk of 5%, leading to a minimal recruitment of 65 patients to obtain 60 evaluable patients, with a null hypothesis of 50% and an alternative hypothesis of 70%. We reported in the submitted version of our paper a 45.71% ORR [95%CI, 33.74-58.06]…in the ITT population.

However, Reviewer 1 was right, and we should have reported the ORR in the 64 evaluable patients (not 65 as we falsely mentioned in the first version, this was corrected in the revised version), in whom we observed 32 responder patients (ORR= 50.0%), close to the null H0 hypothesis set at 50% according to the statistics. Therefore, those results could be considered as enough convincing to reject the null hypothesis of inefficacy, and to deserve further larger phase 3 study as our Fleming design could have authorized.

Reviewer 1 is therefore perfectly right, since our study should be considered as positive according to the statistical design.

We edited our “results” section and mentioned this result more clearly in the “results” section as suggested by the reviewer.

Moreover, the 81.2% Disease Control Rate should be considered as confirmatory of the feasibility of such a design and combination, since very close to the DCR reported in all radio-chemotherapy trials published during the last decade, whereas we used an oral formulation of vinorelbine during the concurrent part of the trial, suggesting a full equivalence between oral and IV formulations of vinorelbine as sensitizers for radiotherapy.
3) Based on the limited efficacy and comparable toxicities of current trial, the conclusion was too affirmative. Authors should consider to revise the conclusion.

Actually, we slightly changed our conclusion, although, again, this trial has to be considered as positive according to the statistical design. However, we underlined one striking result of this trial, the very good esophageal tolerance, and the suggested equivalence between oral and IV formulation of vinorelbine, in terms of survival, for such a regimen totally administered in an outpatient setting, that could lower total costs. We then we added those two messages, which seemed to us important and justified the rationale of this trial.

Minor comments:

1) Median follow-up time was relatively short. Nearly four years have past from the date of data cutoff. It would be better to update the data.

As we mentioned in our discussion with several bibliographic references, and as assessed by Reviewer 2 comments (below), our median survival is strictly comparable to previous larger phase 2 trials.

The main endpoint of the trial was actually ORR and unfortunately, we had no funding for extending follow-up data beyond the planed cut-point date. However our data must be considered as enough mature, since after 37 months of median follow-up, more than 60% of patients deceased and it is unlikely that longer follow-up could have changed any of the reported results in this article.

2) It would be better to add and discuss some references about chemoradiotherapy using cisplatin and vinorelbine. For example, Cancer Sci. 2013 Jan;104(1):93-7.

Thank you for this suggestion and we added this reference to our discussion.

However, this excellent paper, of which first author is actually the Reviewer himself, reports a very high 80% ORR with I.V. vinorelbine plus platinum, and concurrent radiotherapy, contrasting with responses rates published in different phase 2 or 3 trials of chemo-radiotherapy during the last decade, all referenced in our article. We also should keep in mind this trial included a rather different population of patients, since predominantly including adenocarcinoma patients (64%) and only 23.4% of squamous cell carcinoma, whereas our series contained 44.3% of SCC and only 35% of adenocarcinoma, precluding any direct comparison between the two trials.

Quality of written English: Needs some language corrections before being published

The manuscript was thoroughly reviewed by Soumeya Zerouta, an English native-speaking professional, born in London, working at Eltium SARL, and the few spelling/grammar errors were corrected. We feel that language editing fits now with the international standard for scientific publication.
Reviewer 1: Mariano Provencio

We thank reviewer 2 for his comment:

They have evaluated induction chemotherapy with vinorelbine/cisplatin followed by concomitant CT-RT in unresectable stage III NSCLC. The objective ORR of 45.7%, determined by an independent radiologist, was comparable to other studies which have evaluated vinorelbine/cisplatin using the same therapeutic strategy. The ORR was consistent with the median survival of 17.08 months, and the 1-year and 2-year survivals of 68.6% and 37% respectively. These efficacy results are similar to those reported in recent trials. Overall survival rates according to histological type and disease stage was similar.

This comment actually shows that our study reached its goal showing convincingly that oral formulation of vinorelbine could be a credible alternative to IV formulation during radiotherapy with comparable efficacy results and good tolerance. We think such findings have to be reported, since oral vinorelbine is a more recent marketed form of vinorelbine of which registration has been obtained in stage IV NSCLC patients. The main interest of this trial is actually that such formulation could also be used in stage IIIB patients concurrently with radiotherapy, without loss of efficacy, and with a remarkable tolerance, especially in terms of esophagitis. The ability of publishing such results after other limited-size phase 2 trials using oral vinorelbine during the induction phase or the concurrent sequence, will help, for instance, to perform meta-analyses which could show, in the absence of large phase 3 trials, the highly probable equivalence between oral and IV vinorelbine, as sensitizers for radio-chemotherapy.

We also thank Reviewer 2 for recognizing the quality of English language as acceptable, since edited by native-English speaking professional...