Author's response to reviews

Title: Concurrent chemoradiotherapy with tomotherapy in locally advanced non-small cell lung cancer: Phase I, dose-escalation study

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Author's response to reviews: see over
Dear Editor and Referees

Thank you for your comments on the manuscript: Concurrent chemoradiotherapy with tomodotherapy in locally advanced non-small cell lung cancer: Phase I, dose-escalation study.

An English-mother tongue expert revised the manuscript. I did not underline the changes because they were too many. I have underlined all the parts, we changed, according to the two Referees’ comments.

Referee #1

A) “The title could be a little more explicit. From the title....”

I changed the title, now being: CONCURRENT CHEMORADIOThERAPY WITH TOMOTHERAPY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER: A PHASE I, DOCETAXEL DOSE-ESCALATION STUDY, WITH HYPOFRACTIONATED RADIATION REGIMEN

B) Specifically, why would one expect a different MTD for docetaxel when using Tomotherapy vs standard radiation?....

In the Introduction, pag 3 and 4, I added the reference about the study CALBG 30105, in which the arm with Gemcitabine concurrent with high dose conformal radiation treatment was closed for high rate of severe pulmonary toxicity, likely due to larger mean lung doses. In the paper the authors suggest that the radiosensitizing properties of Gemcitabine on normal tissue may have contributed to the higher pulmonary toxicity observed. On this basis, we were concerned that, using a radiosensitizer agent such as Docetaxel concurrent with Tomotherapy, with larger volumes of healthy lung treated with low dose radiation, could lead to a different maximum tolerated dose (MTD) for Docetaxel. For this reason and since at the time we planned the study there was no information available about Tomotherapy concurrent with chemotherapy, we designed a phase I, dose-finding study to determine the MTD of weekly Docetaxel concurrent with IMRT delivered with HT after induction chemotherapy.

C) Another issue inadequately addressed in the introduction is the why choose single agent docetaxel?....

In the Introduction at pag 4, I added the explanation: We chose to study Docetaxel alone combined with concurrent HT, because Docetaxel may enhance both activity and toxicity of radiotherapy and we did not want to have any confounding bias in the results analysis. For this reason we chose to deliver the backbone of systemic treatment for NSCLC, i.e. platinum, in the induction part, using Docetaxel alone in the concurrent study.

D) It is also noted that the authors chose a relatively hypofractionated radiation regimen....

There are two modalities of shortening overall time of radiotherapy without increasing late complications and allowing for better efficacy outcomes: first is two fractions per day, second is using fewer and larger doses. We used the second strategy, with fewer and larger fractions, as specified at pag 7, in the Radiotherapy section, reference 20 and 21.

E) **Bottom of title page in the section Acknowledgement of grant or other financial support.**

We better specified the sentence as suggested: “All the authors declare no competing financial interests.”

F) **In the final sentence of the background statement in the abstract I think I should read...**

I add the final sentence of the background in the abstract: “The goal of the study was to estimate tolerability of Docetaxel concurrent with IMRT and to find the maximum tolerated dose of weekly Docetaxel concurrent with IMRT delivered with HT Tomotherapy after induction chemotherapy with Cisplatin and Docetaxel in patients affected with stage III Non-Small Cell Lung Cancer.

G) **Similarly, in the final statement of the introduction, should read.....**

We added the final statement at the end of the Introduction, pag 4, as suggested: “We designed a phase I, dose-finding study to estimate the tolerability of concurrent Docetaxel with Tomotherapy and to determine the MTD of weekly Docetaxel concurrent with IMRT delivered with HT after induction chemotherapy.”

H) **In the third sentence of the Patients and Methods section it should be “patient with supraclavicular involvement...”**

I corrected “supraclavicular”, at pag 4, in the section Patients and Methods.

I) **In the fifth sentence of the Discussion, it should read “induction chemotherapy strategy has several theoretical advantages...”**

I changed as suggested, at pag 10-11 in the Discussion, “The induction chemotherapy strategy has several theoretical advantages, such as...”

**Referee #2**

1) **This is not a phase I since the authors did not reach a toxic level.....**

You are right, this was not a classical phase I study, because we did not reach a toxic level, stopping the accrual earlier. Phase I studies attempt is to estimate tolerability and characterize pharmacokinetics and pharmacodynamics; often, one of the first steps in evaluating drugs is to to estimate how large a dose can be given before unacceptable toxicity. That was the design of our study. We were very concerned that docetaxel, as a radiosensitizer, could lead to an increase of toxicity of Tomotherapy- in terms of pulmonary toxicity and esophagitis- and there was no published experiences of Tomotherapy concurrent with chemotherapy. That was the reason why we started with a very low dose of weekly Docetaxel and we increased the dose very carefully.
It was already known that 30 mg/m\(^2\)/week Docetaxel is a limit dose concurrent with standard radiotherapy; it decreases to 20 mg/m\(^2\)/week in a continuous schedule when associated with Cisplatin and concurrent radiotherapy (Yamamoto N, 2006). In a palliative setting, from an Italian metaanalysis (Di Maio M et al, JCO 2006) we know that weekly Docetaxel is as effective as Docetaxel every three weeks; from a previous phase I study, we know that Docetaxel 35–40 mg/m\(^2\) weekly for six consecutive weeks followed by 2 weeks of rest is feasible (Hainsworth JD, Burris HA III, Erland JB, et al: Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol 16:2164-2168, 1998).

Our goal was to demonstrate that Tomotherapy concurrent with docetaxel was tolerable and to find the MTD. We overpassed the MTD of Docetaxel concurrent with traditional radiotherapy (30 mg/m\(^2\)) without toxicities. When we reached the weekly dose used in the palliative setting (38 mg/m\(^2\)/week), we stopped the accrual. We do not think to be ethical to add more patients, because we already know that a greater dose, i.e. greater than 40 mg/m\(^2\)/week- according to the Hainsworth paper-, would lead to unacceptable toxicities in terms of bone marrow toxicities.

I added the reference 24, at pag 10, in the Results.

2) The abstract is not complete: no data on PFS and OS....

At pag 2, in the Abstract section, I added data about PFS and OS. We think data are encouraging, to go to a phase II and then eventually, to a phase III, as we say at the end of the Discussion, pag 12: “Although it was not a primary endpoint for this study, the PFS and OS of the patients recruited in the study and who completed the induction and the combined treatment are encouraging, well above the median data obtained in the previous studies with chemo-radiation for locally advanced NSCLC; however they need further validation through phase II, multi-institutional studies and eventually comparative phase III trials.”

3) p5 Fibonacci 3+3 design: please add a reference.

At pag 5 I added the reference (15) as requested.

4) In the Chemotherapy, there is no description of the cisplatin dose neither the docetaxel dose

At pag 6, in the Chemotherapy section, I added the doses.

5) p6: was started 30 minutes after infusion

I specified as suggested: “thoracic radiotherapy was started 30 minutes after infusion.”

6) In Radiotherapy: since patients were seen every week, and tomotherapy allow imaging daily, was there an adaptive radiotherapy performed?

No, it was not and I specified it at pag 7, in the Radiotherapy section, penultimate sentence.
7) p7....background activity was used as a PET criterion for malignancy...What about inflammatory pathology?  

As specified at pag 8, in the “Patients Evaluation” section, we used CT images to produce attenuation correction values for PET emission reconstruction and fused PET/CT presentation, in order to avoid misinterpretation between inflammatory pathology and tumour. Moreover, PET data were interpreted independently of the result of any prior investigation by two nuclear medicine physicians in consensus, expert in oncological imaging.

8) p9 PR after induction had also PR of the combined treatment. Was this second PR larger than the first?  
The first PR was based on all the patients recruited in the study, i.e. 37 patients overall. The second PR is out of 33 patients, those who completed the combined treatment, as specified at pag 10, in the Results.

9) Induction chemotherapy....What about inducing resistance?  
Induction chemotherapy can induce resistance to future systemic therapies, as every systemic treatment, whenever they can not cure; concomitant treatment, consolidation chemotherapy, even adjuvant (systemic) treatment theoretically can induce resistance. However the goal of our treatment was to eradicate/to cure the tumour. As for the adjuvant setting, where the goal is to cure patients, and the possibility to induce resistance with chemotherapy is considered less important than the amount of benefit, we think that the risk of inducing resistance is minor than the benefit.

10) p:11 To our knowledge this are the first data of tomotherapy....  
We corrected the sentence as suggested, at pag 12, in the Discussion.

Yours sincerely,
Alessandra Bearz