Author's response to reviews

Title: Capecitabine and oxaliplatin combined with bevacizumab are feasible for treating Japanese patients at least 75 years of age with metastatic colorectal cancer

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Version: 3
Date: 1 May 2015

Author's response to reviews:

May 1, 2015

Dafne Solera, PhD
Executive Editor,
BMC Cancer

Dear Dr. Solera,

We greatly appreciate your thoughtful comments and kind invitation to resubmit our manuscript (ID: 1037706307157790) titled (revised) “Capecitabine and oxaliplatin combined with bevacizumab are feasible for treating Japanese patients at least 75 years of age with metastatic colorectal cancer.” We revised the manuscript according to the comments. Our point-by-point responses to the comments offered by you and the referees are listed below.

We hope that the revised manuscript is now suitable for publication in BMC Cancer

Best regards,
#Editor#
Your work includes a limited number of cases, and the reviewers have several concerns about the study. Please reply to all the concerns in a carefully manner. In addition, the study is not new (other studies with this type of patients have been published): the only point of novelty is that your cohort include Asian patients. Please do also a revision at grammar and spelling level.

Response: Thank you for your thoughtful comments and kind invitation to resubmit. The manuscript was revised in accordance with your comments and those of the referees, and the English editing was revised by a scientist whose native language is English.

#Referee 1#

Major Compulsory Revisions

1) How was neuropathy/neurotox assessed? Maybe you could briefly state or provide in an appendix what algorithms you have used to manage drug-toxicities, especially regarding neurotoxicity.

Response: Toxicities including neurotoxicity were graded according to the criteria of the National Cancer Institute Common Terminology for Adverse Events (version 4.0). With respect to neurotoxicity, a brief explanation was added to the text (page 11, line 2-9).

2) Give reasons for trial termination in more detail. You say n=14 patients stopped treatment due to AE, please specify further.

Response: The detailed reasons for trial termination due to AEs is now included in the Results section (page 13, line 11-14).

3a) Please comment on your strategy to treat until progression. Many colleagues would treat over 6 months and then stop.

Response: In this study, the end of the protocol treatment was not prescribed. Treatment was repeated every 3 weeks until progression or termination of the study. At most, one patient received 25 cycles of the treatment until progression.

3b) Put your strategy into context cf point 1 and 2.

Response: Thank you for your suggestion. Replies to your comments 1–3 are
reflected in the text.

3c) Neuropathy G3 is defined as „severe symptoms; limiting self care ADL“. 14% of your patients experienced this „endpoint“, which to me seems unacceptable in a palliative setting. Please comment in detail. Was your strategy of dose reductions well chosen?

Response: Five of 36 patients had G3 neuropathy. Our strategy of dose reduction and discontinuation of oxaliplatin was strictly defined in the study protocol and provided in the text as follows: neuropathy G1, continue the initial dose; G2/3, stop and wait until neuropathy disappears or G1; G4 or recurrent G2/3, discontinuation of oxaliplatin. For these five patients with G3 neuropathy, oxaliplatin was terminated during the protocol treatment and capecitabine and/or bev were administrated until disease progression. As you mentioned, 14% of neuropathy seems more frequent compared with earlier studies. However, a pilot study that evaluated the safety of XELOX plus bev in Japan found that the prevalence of neuropathy G3/4 was 17%. Based on these results, the frequency of severe neuropathy caused by XELOX plus bev may be different between Western and Asian patients. This content was added to the Discussion section with appropriate references.

4) What formula did you use for estimations of CrCl? What are the age corrected reference values?

Response: Creatinine clearance was calculated using the Cockcroft–Gault formula and was adjusted according to the patient’s age. This information is now included in the Methods section (page 9, line 9).

5) Text/Discussion – Modify:
- OS in general populations today is >30months (FIRE, CALBG)

Response: The median OS of patients was 22.9 months. As you point out, it was shorter compared with those of large studies (FIRE-3 = 28.7 months and CALGB/SWOG 80405 = 29 months). The main reason for the difference may be that our patients were older than those in previous studies. In an earlier study for a Western population, OS was 20.4 months, indicating that our results can be considered as a reasonable outcome for patients aged #75 years. This information is now included in the Discussion section (page 18, line 15-19).

I miss a discussion on Pharmacokinetic, especially of capecitabine, in general and in the elderly. Is CrCl the only determining factor for toxicity? Differences between populations US vs Europe vs Asia. Role of nutrition? Gender? BMI? And, of course age?

Response: Pharmacokinetics of capecitabine was included in the Introduction section (page 6, line 9 to page 7, line 2). Further, the influences of region on tolerability of XELOX were discussed with appropriate references. Factors other than CCr, such as age, BMI, and sex, were evaluated as potential determining factors for toxicity, and the results were added to the text (page 14, line 7-8).
Please discuss the role of PS and age in CRC (ARCAD data (Lieu et al ESMO 2013) and older data (Folprecht et al AnnOncol 2004))

Response: Thank you for bringing our attention to these interesting papers. Discussion now includes consideration of the role of age and PS, accordingly (page 19, line 1-7).

Minor Essential Revisions
Please give number of patients screened (or state reasons for unavailability)

Response: Basically, we screened patients who were expected to meet the criteria of this study. Accordingly, we enrolled 36 patients who met all of the criteria.

You state: „we recommend more rigorous measurements of baseline values of the cerebrovascular system …:“ Could you please outline your (future) strategy? Is there any evidence or published data to support a more „rigorous measurement“? Please comment

Response: To the best of our knowledge, there is no evidence that supports “more rigorous measurement.” However, hemorrhagic complications represent one of the most serious AEs of bevacizumab. From our experience, we propose considering cervical bleeding as a possible AE of bevacizumab, careful check of central neurological signs, and the unhesitating performance of head CT scan when cervical bleeding is suspected during chemotherapy combined with bevacizumab.

Did you measure cholesterol, triglycerids or glucose? Many reports appearing about capecitabine leading to important increases in the before values. Please comment.

Response: Unfortunately, we have only baseline data for cholesterol, triglycerides, or glucose, not serial data. This information was added to the Discussion section as limitations of this study (page 20, line 2-5).

Please discuss cardiovasc/thromboembolic risk of BEV in more detail esp as 1/36 of your patients had a lethal intracerebral bleeding.

Response: The patient with lethal intracerebral bleeding was a 77-year-old woman with liver and lung metastasis without serious comorbidities, and seven courses of the protocol treatment (XELOX plus bev) were administered using the standard dose. During the eighth course, she lost consciousness suddenly and was diagnosed with intracerebral bleeding revealed by a CT scan and chemotherapy was discontinued. A detailed progress report is provided in the Results section and our suggestions are now included in the Discussion section (page 13, line 17 to page 14, line 1 and page 18, line 3-6).

Delete or replace ref 14 – In my view technical advances in pancreatic cancer surgery do not explain increasing age of a population
Response: Ref 14 was deleted, and the references were reorganized.

Is there any large, randomised trial on QOL Cap vs 5FU? If yes, please cite. If not please give a more balanced view on selecting capecitabine vs 5FU.

Response: Two additional references (ref 7, 8, 10) supporting the potential superiority of capecitabine to intravenous 5-FU for elderly patients were added.

Discretionary Revisions
Language might benefit from review

Response: The manuscript was revised by a scientist whose native language is English.

Personally, I would not discuss stop/go strategies (ref 27) in conjunction with your data

Response: Thank you for your suggestion. We revised the text accordingly.

Personally, I would review the selection of references

Response: We revised the references.

#Referee 2#

This is an interesting phase II study evaluating the tolerance and efficacy of XELOX+Bevacizumab regimen in the front line setting for patients >75yo with untreated mCRC. The study is limited by it’s small sample size. In addition, data is available in the literature evaluating this regimen in older patients (Feliu et al. BJC 2014). This study is reporting similar data on specific population of older Asian patients. This should be clearly stated in the introduction/abstract

Response: Thank you for your favorable comments. As you point out, the main point of this study was addressed by a study of a Western population. Therefore, we state that our study reports analysis of older Asian patients in the Abstract and Introduction.

Major:

1. As a study evaluating treatment of older cancer patient a geriatric assessment would have been of high value to learn about factors that are specific to the older patient population which could affect treatment outcome. Since this data is difficult to obtain retrospectively, it would be interesting to have more information regarding the patient’s co-morbidity index, BMI, and other factors associated with Performance status. (similar to the analysis done with the CCr)

Response: Factors other than CCr, such as ASA score, ASA-PS score, age, BMI, and gender were evaluated as potential prognostic factors for toxicity, and the results were added to the text (page 14, line 7-8).

2. The authors fail to discuss additional papers evaluating treatment of older
patients with mCRC. These include the AVEX study – which evaluated cape+bev vs. cape alone – interestingly this study showed a very similar OS (20.7m) to the one reported in this study, which raises the question regarding the benefit of adding oxaliplatin. Another study that should be discussed is the FOCUS2 study which compared 5FU/CAPE +/- oxaliplatin and did not show any significant benefit to the addition of oxaliplatin. These studies should be included in the discussion and the question regarding the benefit of oxaliplatin should be raised.

Response: Thank you for your thoughtful suggestion. Results of AVEX and FOCUS2 trials were discussed in the text to assess the benefit of oxaliplatin (page 17, line 8-15).

3. The authors report TTF of 7 months. This outcome measure is not clear, and is not defined in the methods. It is not clear what is the difference between TTF and PFS. Is the meaning to time until treatment discontinuation? Furthermore, it is clear that most patients were not able to stay on XELOX+bev for the full study period (median 5 cycles). There is no information in the paper regarding what patients got after they were taken off oxaliplatin, this is important when evaluating efficacy.

Response: In our study, time to treatment failure (TTF) was defined as the time from randomization to discontinuation of treatment for any reason, not only disease progression but also treatment toxicity, patient preference, or death. This content is now included in the Methods section (page 11, line 15-17). We now state in the Discussion that discontinuation of treatment may be the result of toxicity, patient preference, or a physician’s reluctance to continue therapy. Information about treatment after discontinuation of oxaliplatin is included (page 16, line 3-5). Fourteen patients received the protocol treatment after discontinuation of oxaliplatin, capecitabine with bevacizumab for 12 patients, and capecitabine alone for two patients.

4. The rates of AEs reported in the study are quite high (neuropathy of 13.9%, is higher than seen in other studies). This may be related to the small sample size in which even small number of patients would result in high percentage of the total. However, the authors fail to describe what method was used to evaluated toxicity in the study in the method section. This is important to evaluate this in relation to other studies.

Response: Toxicities including neurotoxicity were graded according to the criteria of the National Cancer Institute Common Terminology for Adverse Events (version 4.0). With respect to neurotoxicity, a brief explanation was added (page 11, line 2-9).

Minor:

1. Abstract: missing data regarding the number of patients on the study, and some information regarding the patient’s characteristics.

Response: The following information was added to the abstract. Thirty-six
patients met all eligibility criteria and received at least one course of the planned treatment. Median age was 78 years (range 75–86 years), male to female ratio was 21:15, and colon cancer to rectal cancer ratio was 24:12.

2. Introduction: Page #7 line #7 – there is newer data from the recent CALGB 80405 study of longer overall survival of mCRC patients. Line #16 wrong reference for the XELOX study.

Response: We revised the references throughout the manuscript.

3. Methods: Please include how many centers participated in the study. As noted above – definition of TTF and the tools used to assess toxicity should be included.

Response: The number of participating institutes, definition of TTF, and the tools used to assess toxicity are now included in the Methods section.

4. Results: The use of acronym CCr for the analysis of toxicity – please clarify if this is creatinine clearance or baseline creatinine?

Response: CCr was defined as creatinine clearance using the Cockcroft–Gault formula in the Methods section (page 9, line 9).

5. Discussion:

a. The AVEX study is included in the references and listed under a few of the sentences regarding prior studies with XELOX – this is incorrect since the study did not include oxaliplatin.

Response: We revised the references throughout the manuscript.

b. The authors use the term “survival benefit of XELOX” multiple times throughout the article. This seems in appropriate since the study did not compare XELOX to any other regimen. Furthermore, as noted above, the results from the AVEX study (phase III RCT trial) are not much different, which raises a question regarding the benefit of oxaliplatin.

Response: We thank the Referee for these thoughtful comments. We revised the text and state in the Discussion the limitation that we were unable to determine the survival benefit of XELOX. The median OS of patients was 22.9 months. As you indicate, this is somewhat shorter compared with large studies (FIRE-3 28.7 months and CALGB/SWOG 80405 29 months). The main reason for the difference may be attributed to patients in our study being older than those in the previous studies. In an earlier study of a Western population, OS was 20.4 months, indicating that our results can be considered as a reasonable outcome for patients aged #75 years. This information is now included in the Discussion section (page 18, line 15-19).

c. Page #17 line #4 – the authors state that oxaliplatin can be given without a central venous port. This is not correct, there is a risk of extravasation with oxaliplatin and at least in our institution we give it with a central access.
Response: We revised the text accordingly. Oxaliplatin is easier to use than cisplatin, because it does not require extensive hydration and thus can be administered to outpatients. In addition, potential advantages of capecitabine over intravenous 5-FU are stated in the text (page 6, line 18 to page 7, line 2).

6. Table 3: This table is not clear – it most likely should be a table with the rates of response. However it includes treatment cycles and dose intensity. The section of the treatment cycles is very vague, is that what patients got after the stopped oxaliplatin? The dose intensity does not make sense – it seems that the dose intensity of bev was 1.0, yet above that 10 patients received XELOX alone and 2 patients received capecitabine alone.

Response: Table 3 was simplified to increase clarity. Relative dose intensity (dose intensity/planned dose intensity × 100) of the three drugs was calculated during the initial protocol regimen (XELOX +bev).