Author’s response to reviews

Title: A retrospective feasibility study of biweekly docetaxel in patients with high-risk metastatic castration-naïve prostate cancer

Authors:
Sang Eun Yoon (dtd43@daum.net)
Youjin Kim (yujin.kim@samsung.com)
Jangho Cho (jangho.cho@samsung.com)
Minyong Kang (m79.kang@samsung.com)
Hyun Hwan Sung (hyunhwan.sung@samsung.com)
Hwang Gyun Jeon (hwanggyun.jeon@samsung.com)
Byoung Chang Jeong (bc2.jung@samsung.com)
Seong Il Seo (seongil.seo@samsung.com)
Seong Soo Jeon (seongsoo.jeon@samsung.com)
Hyun Moo Lee (hyunmoo.lee@samsung.com)
Han yong Choi (hanyong.choi@samsung.com)
Su Jin Lee (ssjj.lee@samsung.com)
Se Hoon Park (hematoma@skku.edu)

Version: 2 Date: 15 Mar 2019

Author’s response to reviews:

BMC urology
RE : submission BURO-D-18-00379R1

Dear editorial office,

Our revised manuscript titled, “A retrospective feasibility study of biweekly docetaxel in patients with high-risk metastatic castration-naïve prostate cancer” is enclosed for consideration for publication as an original article in “Journal of cancer”.

Our responses to the reviewers are detailed below.

We appreciate the thoroughness of the reviewers and hope that these changes adequately address their concerns. These changes were indicated with blue in the revised manuscript.

Best Regards,

Editor Comments:

Currently, your manuscript contains an unacceptable overlap in text with previous literature. In line with our policies please rewrite the following sections in original language (even if the text is from your own previous work): the abstract, background, methods section, lines 166-177, 175-177, 184, and 217-220.

► Thank you for your comments. I agree on your opinion.

According to your comments, we modified the paragraphs as follows;

<166-177, 175-177>“Biweekly docetaxel showed manageable toxicities including all grades (Table 2). The most ordinary adverse events were alopecia (74%), nail changes (42%), and constipation (31%). Hematologic adverse events presented rarely. There were five patients required blood transfusion due to anemia and/or thrombocytopenia, but they did not receive hematopoietic growth factors. One patient died of respiratory failure induced pneumonia complication after completing the fourth cycle chemotherapy.

There was no complete clinical response in the current study. 31 patients evaluated for radiologic responses and seventeen patients (55%, 95% CI: 46–64) presented partial responses. and ten patients achieved stable disease. Finally, 87% of the overall patients obtained adequate disease control.

33 patients (94%) demonstrated PSA response (> 50% decrease from baseline), and 49% patients appeared radiologic response. Median PFS was 13.6 months (95% CI: 6.7–20.4). Median OS was not reached, but the OS rate at one year was identified as 75%. We offered salvage treatment to seven patients following development of CRPC.

Second-line chemotherapy such as abiraterone acetate (three patients), enzalutamide (two patients), cabazitaxel (one patient), and docetaxel rechallenge (one patient) was initiated in patients after ADT plus early docetaxel. 11 patients were undergoing palliative radiotherapy.”

<184>
“Although there are newly developed numerous treatment options for advanced prostate cancer, overall outcomes of metastatic prostate cancer patients are dismal.”

“A prospective trial is needed to confirm the efficacy and toxicity of the early docetaxel chemotherapy in combination with ADT in Korean men with mCNPC.

ADT plus biweekly-administered docetaxel appeared to be tolerated and effective in patients with high-risk mCNPC comparable with CRPC. Our results suggest that a biweekly docetaxel chemotherapy regimen is considered to have manageable toxicities and to yield acceptable results compared to a thrice-weekly docetaxel regimen.”

BMC Urology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

►Thank you for your comments. We have confirmed.

Reviewer reports:
Antonello Veccia (Reviewer 1): The article is overall well written and interesting. In fact, it investigates the safety profile of a modified schedule of biweekly docetaxel in hormone-sensitive PC, that represents a setting in which prostate cancer patients need to receive therapy due to high disease burden but at the same time need to preserve quality of life.

I list only a few point that could to be improved.

1. In the Background paragraph, the author should more widely discuss of docetaxel role in hormone-sensitive PC.

►Thank you for your comments. I agree on your opinion.

According to your comments, we modified the paragraphs as follows;

“Although surgical or medical castration is considered standard treatment in castrate-naïve prostate cancer (CNPC), some patients with extensive metastatic (i.e., high-risk) disease at diagnosis, including visceral or bone involvement beyond the axial skeleton, have shorter survival times [12]. It is not enough to start standard hormone castration treatment alone to high tumor volume at CNPC diagnosis. The previous randomized phase III trials were conducted using either six or nine cycles of docetaxel 75 mg/m2 every three weeks in the CNPC setting
[13-15]. Their results led to early change to ADT in high-risk CNPC in most guidelines published by the oncology societies [16, 17].”

2. In both Methods and Discussion paragraphs, the authors should specify how the response was evaluated (chest x-ray and abdomen CT scan? Chest and abdomen CT scan? Bone scan in all patients?).

►Thank you for your comments.

In the section that suggests the treatment, we already described the follow up examination and duration.

3. In the Results, a few data were reported on responses; a table could be added for making the type of response more immediate.

►Thank you for your comments. I agree on your opinion.

According to your comments, we added the table;

Supplementary table 1.

<table>
<thead>
<tr>
<th>Radiologic Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>17 (54.8)</td>
</tr>
<tr>
<td>SD</td>
<td>10 (32.3)</td>
</tr>
<tr>
<td>PD</td>
<td>14 (45.2)</td>
</tr>
<tr>
<td>NE</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td>DCR *</td>
<td>27 (87.1)</td>
</tr>
</tbody>
</table>
4. About table 2, reporting number of patients and corresponding percentage of toxicities grades should be more useful and of immediate impact.

Thank you for your comments. I agree on your opinion.

According to your comments, we modified the table 2. as follows;

<table>
<thead>
<tr>
<th></th>
<th>Grades 1/2</th>
<th>Grades 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (22.9)</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (17.1)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (11.4)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>26 (74.3)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (17.1)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (11.4)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (14.3)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>8 (22.9)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>7 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (8.6)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (31.4)</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>9 (25.7)</td>
<td>0</td>
</tr>
<tr>
<td>Nail changes</td>
<td>15 (42.9)</td>
<td>0</td>
</tr>
</tbody>
</table>

Tanya Dorff (Reviewer 2): The authors describe a retrospective cohort of men with castration-naïve prostate cancer (i.e. mHSPC) treated with an alternate dosing schedule for docetaxel - q2 weeks instead of q3 weeks. Unfortunately, there is not a clear hypothesis, the reader believes the hypothesis was that q2 weekly dosing might be less toxic but similarly effective, but this is not clearly laid out. It is possible the hypothesis was that Korean men with mHSPC might have differential results with docetaxel in the HSPC setting based on a statement in the discussion.
The authors conclude that the biweekly regimen is feasible (though this was already shown in the CRPC setting) but do not draw a conclusion as to what further study would need to be done, what endpoints would need to be achieved, in order for this to become an alternative option to standard docetaxel as per CHAARTED.

►Thank you for your comments.

According to your comments, we deleted the last paragraph of the discussion.

A prospective trial is needed to confirm the efficacy and toxicity of the early docetaxel chemotherapy in combination with ADT in Korean men with mCNPC.

Because the results of the present study suggest tolerability compared with standard thrice-weekly docetaxel, we have initiated a prospective study evaluating this biweekly regimen (ClinicalTrials.gov, NCT03061643).

Strengths of this manuscript include prior publications on the biweekly regimen and uniform treatment and follow up of patients. weaknesses include a small sample size, lack of compelling rationale and clear explanation of impact of results.

►Thank you for your comments.

According to your comments, we modified the paragraphs as follows;

“The major limitations of our retrospective study include small sample size, lack of enforcing rationale and clear explanation of impact of results. Within the limitations of our study, we demonstrated that early chemotherapy with biweekly docetaxel regimen resulted in tolerability and activity in patients with high-risk CNPC. “

Minor

In the background the authors fail to mention that TAX-327 contained a weekly docetaxel arms, which was found to be less effective than the 3 weekly dosing. is there any hypothesis why 2-weekly dosing would be better than 3-weekly, while weekly was not better? is the hypothesis that Korean men may not benefit from Docetaxel (this is hinted at in a statement in the discussion) and so the study was undertaken to determine whether they do benefit?

►Thank you for your comments. I agree on your opinion.

“Docetaxel is commonly administered at a dose of 75 mg/m2 every three weeks established by the results from the TAX-327 study [5, 6], in which once every three weeks docetaxel (median : 19.2 months, 95% CI, 17.5 to 21.3 months) conferred a definite survival benefit over weekly docetaxel for 3 weeks (median : 17.8 months, 95% CI, 16.2 to 19.2 months).
In Asian countries, there was better survival benefit in every three weeks administration (12.5 months) than every week administration (8.0 months). No grade 3 or 4 neutropenia was showed in once weekly for 3 weeks, but Gr 3/4 neutropenia was observed more frequently about 75% of patients with CRPC who were treated with once every three weeks docetaxel [7]. Based on a pharmacokinetics study conducted in Japan [8] and consideration of efficacy and toxicities in the management of solid tumors in a palliative setting [9], docetaxel is most commonly administered in Korea and Japan at a lower dose (i.e., 60 mg/m2 every three weeks).”

the last paragraph in the results does not make sense. the last sentence of the preceeding paragraph should be connected to the last paragraph. why did only 7 patients receive treatment upon development of CRPC? were the others transitioned to hospice? if so it would seem the OS would be lower at 1 year. the others were progressing but not enough to warrant initiation of additional treatment perhaps?

► Thank you for your comments. I agree on your opinion.

According to your comments, we deleted the last paragraph of the results.

“We offered salvage treatment to seven patients following development of CRPC. Second-line chemotherapy such as abiraterone acetate (three patients), enzalutamide (two patients), cabazitaxel (one patient), and docetaxel rechallenge (one patient) was initiated in patients after ADT plus early docetaxel. 11 patients were undergoing palliative radiotherapy.”

Major

the discussion should be re-written to more clearly lay out the background and why this study was performed. Ex: docetaxel q3 weekly became a standard therapy based on survival benefit over mitoxantrone in mCRPC. then it was shown to prolong survival in mHSPC (or CNPC, as the authors label it) in CHAARTED/STAMPEDE. however toxicity resulted in discontinuation of XX% of patients in CHAARTED/STAMPEDE. (do some patients opt out altogether due to toxicity?) docetaxel q2 weekly has been found to have better tolerability. etc etc

the discussion would also benefit from re-writing for clarification in the section that follows as well. it seems the authors aim to contextualize their OS results with those of CHAARTED/STAMPEDE but this section is lengthy and unclear. The authors then attempt to compare toxicity, and here again things could be stated more clearly. in CHAARTED there were XX% with grade 3 or 4 adverse event [name it] whereas in this small experience YY% had grade 3 or 4. The authors could comment on how many patients required GCSF support or other similar parameters.

in the discussion, as mentioned earlier, there seems to be some hint that docetaxel with ADT may not be beneficial in Korean men. what is the basis for this? if the authors feel that Asian prostate cancer patients were not well represented in the q3 weekly docetaxel trials, that would help support this line of reasoning. this could be added to the background. also, if there have been any
data suggesting differential outcomes or toxicity, this should be added to background and discussion. otherwise, the sentence that "a prospective trial is needed to determine whether early docetaxel chemotherapy in combination with ADT is beneficial in Korean men with mCNPC" doesn't fit with all that comes before it. based on CHAARTED and STAMPEDE we can say that "men" with CNPC benefit, which should include Korean unless there is some reason to believe otherwise. perhaps the authors were trying to say prospective study is needed to determine whether biweekly docetaxel is more beneficial than q3 week docetaxel? the reader is left with many questions after the discussion.

the first sentence of the Conclusion section can be removed as it does not have a conclusion in it. to state that biweekly docetaxel should be an option based on 35 patients is an overstatement. the authors should justify why further study of this dosing regimen is the most important question to be answered after CHAARTED/STAMPEDE - are there compelling toxicity reasons why the biweekly regimen should be studied to see whether it could become an alternative to q3 weekly dosing? would the endpoint for such a trial be non-inferiority? and QOL?

► Thank you for your comments. I agree on your opinion.

According to your comments, we modified the discussion as follows;

“There are newly developed numerous treatment options for advanced prostate cancer, but it is not yet possible to replace all of the docetaxel [17]. The standard docetaxel regimen (75 mg/m2 every three weeks plus prednisone) should significantly improve overall survival for long time in metastatic CRPC, but more often grade 3-4 adverse events. In the current study, we reported that docetaxel 40 mg/m2 every two weeks plus prednisolone was similar in efficacy and manageable toxicities compared to previous studies.

Docetaxel administrated 75mg/m2 every 3 weeks is mostly used at the standard of chemotherapy of mCRPC. However, therapy-related adverse effects and treatment related mortality were prevalent in elderly and fragile patients to receive standard regimen. Although the response of docetaxel 75mg/m2 every 3 weeks schedule was favorable, it did not show the good overall survival for these patients. [19].

In a retrospective study, we evaluated the feasibility of biweekly docetaxel 40 mg/m2 and compared with 75 mg/m2 every 3 weeks for mCRPC. Their median age was 68 years (range, 52-84). The patients received biweekly docetaxel 40 mg/m2 presented similar TTP (5.0 months vs 4.2 months, p-value=0.530) and minor incidence of Gr 3/4 adverse events. This result exhibited one of the treatment schedule options for mCRPC [11].

There were no comparable studies of biweekly docetaxel 40 mg/m2 and 75 mg/m2 every 3 weeks for mCNPC. In the CHAARTED study, the researchers compared the efficacy and toxicity of docetaxel (at a dose of 75mg/m2 every 3 weeks for six cycles) plus ADT and ADT alone of 790 mCNPC patients. The docetaxel plus ADT regimen demonstrated better outcomes than ADT alone (57.6 months vs. 44.0 months; P<0.001) in patient with mCNPC. The current outcome was not equally comparable with the CHAARTED due to the follow-up period was
shorter, as so we need a long-term follow-up period to present the outcome including OS. However, adequate response rate reached 87% even in the short observation period, we considered one of the treatment options.

We already know that the high tumor burden is a poor prognostic factor. Each clinical study had also dealt with the correlation survival and high tumor burden. In the subgroup analysis from the CHAARTED study, a high volume of metastases was defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis. There were 57 (14.4%) patients with visceral metastasis who had poor median OS (49.2 months) than in all CNPC patients (57.6 months) [13, 14]. In the GETUG-AFU15 study, the median OS was approximately 62.1 months in the mCNPC patients, and less than 36 months in the mCNPC patient with high-volume, high-risk disease [14].

In current study, we included that all patients had high-volume CNPC such as visceral metastasis (49%) and bone metastasis (51%). The result (median PFS: 13.6 months, 95% CI: 6.7–20.4) was not as bad as expected from high risk. However, it is limited in interpretation of the PFS because of small sample size and short follow up period. Based on recent randomized trials [13-15] and our data, the addition of docetaxel to ADT is recommended for patients with high-risk, metastatic CNPC who are medically-fit enough to tolerate docetaxel.

In the CHAARTED, the total dosage of docetaxel 75mg/m2 every 3 weeks for six cycles was 450 mg, and the period of administration was 18 weeks. Similarly, the total dosage of the 40 mg/m2 every two-week regimen was 480 mg, and the period of administration was 24 weeks. There was a little difference in docetaxel dosage or administration period between the two regimens. Nevertheless, it showed a different pattern of drug toxicities between the two studies. Approximately 12.1% of patients in the CHAARTED had grade 3 or 4 neutropenia and 6.1% had grade 3 or 4 febrile neutropenia. [13, 14]. In present study, the most common hematologic toxicity of any grade was anemia (n = 12), and grade 3 or 4 hematological adverse events occurred infrequently. There was no big distinctness in the dose and the toxicity was lower in 40 mg/m2 every two-week regimen. So, we could suggest A as other administration schedules on these results.

The major limitations of our retrospective study include small sample size, lack of enforcing rationale and clear explanation of impact of results. Further accumulation of cases with longer follow-up periods is necessary. Within the limitations of our study, we demonstrated that early chemotherapy with biweekly docetaxel regimen resulted in tolerability and activity in patients with high-risk CNPC.

ADT plus biweekly-administered docetaxel appeared to be tolerated and effective in patients with high-risk mCNPC comparable with CRPC. Our results suggest that a biweekly docetaxel chemotherapy regimen is considered to have manageable toxicities and to yield acceptable results compared to a thrice-weekly docetaxel regimen.”

We appreciate the thoroughness of the reviewers and hope that these changes adequately address their concern. These changes were indicated with red in the revised manuscript.
Correspondence: Se Hoon Park, MD, PhD

Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-3459; Fax: +82-2-3410-1754
E-mail: hemotoma@skku.edu