Author's response to reviews

Title: Prognostic impact of clinicopathologic parameters in stage II/III breast cancer treated with neoadjuvant docetaxel and doxorubicin chemotherapy: paradoxical features of the triple negative breast cancer.

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Version: 2 Date: 15 August 2007

Author’s response to reviews: see over
August 15, 2007

Editor
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Dear Dr. Scott Edmunds PhD., Assistant Editor of BMC Cancer

Manuscript number: MS 1637075178145274

We wish to express our gratitude to you and the reviewers for the consideration and thorough review of our manuscript entitled “Prognostic impact of clinicopathologic parameters in stage II/III breast cancer treated with neoadjuvant docetaxel and doxorubicin chemotherapy: paradoxical features of the triple negative breast cancer”. We have revised our manuscript based on the reviewers’ comments, which we feel has clarified and strengthened the paper considerably.

Here we have addressed the concerns of the reviewers on separate pages, as well as our responses to specific comments. I hope that you and reviewers will find these alterations satisfactory. We look forward to having our manuscript published in “BMC Cancer”.

Best wishes,

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Author’s response to reviews

Thank you for your interest and your valuable feedback. We revised the manuscript and yellow highlighted lines were revised text.

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Title: Prognostic impact of clinicopathologic parameters in stage II/III breast cancer treated with neoadjuvant docetaxel and doxorubicin chemotherapy: paradoxical features of the triple negative breast cancer.

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Version 1 date 2007-08-15

Reviewer1: Daniela Kandioler

Discretionary Revisions
1) Would be nice to discuss the difference between radiologic (7 pat) and pathologic complete response (11 pat) and mention the differences seen in other studies.

Response>
     We revised our manuscript as follows according to your recommendation in page 8 line7. “The overall radiologic response rate (RR) was 68.9% including 7 complete response (4.8%) and 93 partial response (64.1%) (Table 2). All 7 radiologic complete responder showed pCR and four patients who showed radiologic residual lesion were turned out to pCR. Consequently, eleven patients (7.6%) achieved a pCR (Table 2).”

     We evaluated response using breast MRI taken pre and post chemotherapy. Breast MRI is more accurate than breast USG in visualizing residual tumor extent after neoadjuvant chemotherapy (NAC). In the present study, 4 patients who showed radiologic residual lesion were revealed to be pCR. Similar discrepancy between MRI and pathology was observed in the other study. Akazawa et al (Breast J 2006:12:130-7) reported that the difference in tumor length between MRI and pathology after NAC was less than 2 cm in 36 of 38 patients and two patients...
showed discrepancy more than 2cm. However, comparing with breast USG, MRI has strong power to predict pCR.

2) What about breast conserving surgery: 69% clinical response rate resulted in a 36% breast conservation rate. Would be interesting to mention the overall institutional breast conservation rate.

Response>

Usually in Korea, ultrasound based breast cancer screening test is popularly performed, about 70% of breast cancer patients who received curative breast cancer surgery were stage 0 to stage II. Overall breast conserving surgery (BCS) rate of our institution is 42% from year 2002 to year 2004 (734 BCS among 1750 breast cancer surgery for 3 years). Although 36% of breast conservation rate is lower than our institutional breast conserving surgery rate, if you consider that the median tumor size of this study population was 5 cm which is relatively large for Asian woman who have small breast, most of patients (84.1%) were clinical stage III at the time of initial diagnosis. The 36% of BCS rate is quite high rate for this population. Mention about BCS rate has added in page 8 line 6: “The median tumor size was 5 cm which is relatively large for Asian woman who have small breast. The breast conserving surgery rate was 35.9%.”

3) The expression of p53 was not different in triple neg and positive. It has been suggested that the better response of triple neg to taxane based regimens might be based on the higher incidence of p53 mutations in this subgroup. In this context the technological bias of p53 IHC in detecting p53 mutatants and p53 sequencing technique for detection of mutations should be adressed.

Response>

That is an adequate and important point because functional mutation of p53 was not reflected by quantitative IHC method. The discussion section has been revised to address these points (page 11, line 7): “In our results, overexpression of p53 failed to show clinical significance in neoadjuvant setting. However, p53 mutation which was associated with response to neoadjuvant chemotherapy [13] was not in agreement with p53 overexpression measured by quantitative immunohistochemistry. Additional mutational study of p53 is needed to clarify correlation between p53 and clinical outcomes.”
Reviewer2: Frederique PENAULT-LLORCA

Major Compulsory Revisions
1) Concerning the results it is difficult to understand the choice of the data for the response rate to neoadjuvant treatment in table 3 it is radiological response rate, in table 4 it is clinical response rate BUT pCR is not clearly used in the correlation and when we hardly find it in the table it is not correlated to survival but to radiological response rate (table 4).

Response>
* ‘Clinical response’ and ‘radiologic response’ were usually used together in many research articles due to differences of measurement modality, and sometimes both were confused. In our study, the term of ‘radiologic response’ is more precise term rather than ‘clinical response’ because we used breast MRI and chest CT for response evaluation. We corrected the term of ‘clinical response’ to ‘radiologic response’ in table 3,5,7 according to your recommendation. It is merely descriptional problem. We corrected this in order to avoid making readers confused, as mentioned in reviewer’s comment.
* In the present study, pCR was failed to show prognostic value as mentioned in discussion (page 11, line 20). Probably, low pCR rate and short follow up duration (median 18.6 months) might contribute to this result. Three cycles of neoadjuvant chemotherapy would lead to low pCR rate compared with 8 cycles in NSABP B-27 (which is sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide). And median tumor size of 5 cm is quite large compared with other neoadjuvant clinical trial for ‘operable’ breast cancer. Despite of this limitation, we believe these data have the value because other molecular marker showed statistical significance even though low pCR and short follow up duration.

2) And triple negative status is correlated to radiological response rate (which is not clearly defined in the material and methods section (we find that it is correlated to pCR only in the text why not in table 3?))

Response>
To clarify radiologic response (RR), we described detailed definition of RR in material and method section (page 6, line 19). We evaluated radiologic response using pre and post breast
MRI and chest CT by RECIST criteria. Radiologic response was evaluated using breast MRI for primary breast cancer measurement and chest CT for lymph node measurement by RECIST criteria [17] as follows; complete response was defined as the complete disappearance of all assessable lesions; partial response as a >30% reduction in the sum of the longest diameters of all measurable lesions; stable disease as a <30% reduction or a <20% increase in the sum of the longest diameters of all measurable lesions; and progressive disease was defined as >20% increase in the area(s) of original measurable lesion or the appearance of a new lesion.”

We added pCR in Table 3 according to your recommendation and the following sentences in page9 line 2. “Table 3 compares radiologic RR and predictive factors. pCR was correlated with radiologic RR (p=0.018). pCR and radiologic RR according to ER/PR/c-erbB2 are summarized in Table 4.”

4) Usually pCR is used in the neoadjuvant trials as the primary goal and the predictive /prognostic markers are evaluated towards pCR why is it not the case in this study?

Response>

* The present study was designed in year 2001 and started in 2002. At that time the aim of this study was to conversion of inoperable breast cancer to operable breast cancer or increasing the rate of breast conserving surgery for young breast cancer patients (median age of this study is 45 yr.) who should received MRM otherwise received neoadjuvant chemotherapy. The primary goal was radiologic (clinical) response rate in marginally operable breast cancer patients who had locally advanced (large primary mass or fixed axillary node or N3 disease). Therefore, we evaluated the predictive and prognostic markers towards the radiologic response (early response to neoadjuvant chemotherapy). Three cycles of neoadjuvant chemotherapy would lead to low pCR rate compared with 8 cycles in NSABP B-27 (which is sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide for pCR). And median tumor size of 5 cm is quite large compared with other neoadjuvant clinical trial for ‘operable’ breast cancer. Despite of this limitation, we believe these data have the value because other molecular marker showed statistical significance even though low pCR and short follow up duration. We expect that pCR will become statistically significant if follow up duration is prolonged.

5) Then the pCR or response levels in other categories i.e. HER2+, ER+ and/or PR+ should also be presented
pCR and response rate according to ER/PR/HER-2 were summarized in new table (Table 4)

6) The pCR rate is this study are low 7.6% it is frequently close to 15% with taxanes (papers from MD Anderson, Amat Br J Cancer 2003). In this study the chemotherapy dose might be not sufficient: only three cycles.

Response:

1) The reviewer pointed out appropriate and important point in current practice setting that we also think about during analysis. Although optimal cycles of neoadjuvant chemotherapy (NAC) have not yet established, recently, many researchers believed that 4 or more cycles would be suitable by analyzing many recent articles. We designed this protocol in year 2001 and started in 2002, when optimal cycle of NAC had not reached consensus, 3 or 4 cycles of neoadjuvant chemotherapy was recommended as a practical guideline and totally 4 (eg. AC #4) or 6 (eg. FAC #6 or FEC #6) cycles of anthracycline based adjuvant chemotherapy or 8 cycles of adjuvant chemotherapy (AC #4 → T#4) was recommended for node positive breast cancer. Therefore, we designed this perioperative DA #3 op. → DA #3, that is, 6 cycles of docetaxel and doxorubicin chemotherapy was planned for the enrolled patients which is sufficient treatment for node positive breast cancer. Other group in Korea, Han S et al (breast cancer res treat 2006:98;57-61) reported that this regimen (DA#3 op → DA#3) was effective.

2) Three cycles of neoadjuvant chemotherapy would lead to low pCR rate compared with 8 cycles in NSABP B-27 (which is sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide for pCR). And median tumor size of 5 cm is quite large compared with other neoadjuvant clinical trial for ‘operable’ breast cancer which also affect to the pCR. Despite of this limitation, we believe these data have the value because other molecular marker showed statistical significance even though low pCR and short follow up duration.

3) Korean physicians have difficulty to free from insurance reimbursement. There has been limitation in designing protocol for expensive docetaxel at that time and only 3 cycles of docetaxel based neoadjuvant chemotherapy was reimbursed.

4) The principal goal of our NAC was conversion of inoperable to operable breast cancer rather than breast conserving surgery (BCS) because significant portion of patients were advanced stage. In our study population, 122 patients (84.1%) were stage III and 65
patients (44.8%) were clinical N2 or N3. Owing to small and dense breast of Korean women, significant portion were inoperable even though median tumor size was 5cm. Furthermore Korean breast cancer patients showed high proportion of young breast cancer (Ahn et al. JCO 2007:25; 2360-2368) as well as diffuse breast cancer. When we designed this protocol, conversion of inoperable to operable was more important than BCS.

7) How many patients did receive adjuvant chemotherapy after surgery? did this impacted the OS and DFS. Did the patient with pCR received adjuvant treatment?

Response>

The adjuvant therapy was described in Method section as in page 5 line 13 “After completion of neoadjuvant treatment, the patients underwent primary surgery and received three more cycles of docetaxel and doxorubicin as adjuvant chemotherapy, followed by radiation or hormonal therapy if indicated”

We also described additional information about adjuvant chemotherapy in the result section (page 8, line 12). “Of 145 patients, 138 patients including patients with pCR received three more cycles of docetaxel and doxorubicin as planned adjuvant chemotherapy. Three patients who showed progressive disease and 4 patients who were unacceptable to docetaxel received different adjuvant chemotherapy including FAC (5-fluorouracil, doxorubicin, cyclophosphamide), AC (doxorubicin, cyclophosphamide) or CMF (cyclophosphamide, methotrexate, 5-fluorouracil) after curative surgery.”

Minor Essential Revisions
1) The IHC methods used in this study need more description: a table with the name of the antibodies, the dilution ect…

Response> We already have 7 Tables in our manuscript, therefore, we have described information in detail about IHC in Methods section. (Page6, line 12)

“The primary antibodies and the dilution factors used were;

ER (Dako Corporation, Carpinteria, CA, USA; 1:50)
PR (Dako Corporation; 1:50)
p53 (Dako Corporation; 1:1200)
bcl-2 (Dako Corporation; 1:50)
Ki-67 (Dako Corporation; 1:800)
All primary antibodies were mouse monoclonal antibodies. Biotinylated anti-mouse antibody was used as secondary antibody and streptavidin horseradish peroxidase (Zymed laboratories, San Francisco, CA, USA) methods were used.

2) Then we also need to know more about the ethics (the protocol was approved by a board but did the patients signed a inform consent?),
Response> Yes, the protocol was reviewed by IRB of Seoul National University Hospital (SNUH) and received signed chemotherapy permission for inform consent. We added the following sentence “Recommendations of the Declaration of Helsinki for biomedical research involving human subjects were also followed.” This has been mentioned in material and methods section (page 6, line 8).

3) the discussion is also too long when compared to the length of the paper and should be shortened. The discussion about the prognosis value of pathologic stage after treatment should take into account the work by Chollet P et al Br J Cancer 2003).
Response> We have tried to shorten it as much as possible; however, it is very difficult to shorten it more than that. We have tried to trim it as much as possible, but feel that it is impossible to make it any shorter without putting part of it in an electronic appendix. The discussion section has been revised to address the work by Chollet P et al Br J Cancer 2003). (page 12, line 9)

Discretionary Revisions
1) The tables should be reviewed in the light of the comments
Response> The tables have been revised including term of clinical response.

2) The writing is acceptable, but avoid to start a chapter by table4 shows
Response>
The text has been rewritten (Page 9, line 7)
Table 4 shows the results of univariate analyses for RFS and OS.
→ The results of univariate analyses for RFS and OS were shown in Table 5.

Dear Editor

● Reference number 33 has been added (page 21).
● Reference number 36 has been changed because abstract which was presented in SanAntonio has published a short time ago (page 21).
● In the acknowledgement section, the fund name was added. We apologize for these typographical errors

Please feel free to contact me if there is any problem or question. Thank you very much for your consideration of our manuscript