Author's response to reviews

Title: Safety and survival effect comparision of adjuvant tamoxifen and toremifene in premenopausal patients with ER/PR positive breast cancer: a retrospective cohort study

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Author's response to reviews: see over
Cover letter

Dear editor,

Thank you very much for giving us pertinent suggestions and now we are glad to answer questions raised by reviewers point by point as follows.

Dr. Patrick’s questions: Major Revisions

1 The language which is used is not correct English and this needs improved upon
Yes, we had tried our best to improve our English writing.

2 How well are large numbers of excluded patients balanced between groups
From figure 1, 810 patients were confirmed to be premenopausal before surgery. Among the excluded 358 patients, 43 quit after a few months (less than one year) of TAM or TOR (23 in TAM, 20 in TOR) and they are balanced between groups (p=0.961). As to the other 315 patients, we think they do not influence the results completely because they do not meet the eligible criteria of inclusion.

3 Statistics: there is a 13% difference in local treatment modality (mastectomy versus breast conservative surgery). Tamoxifen users clearly had a higher tumor load which might explain small differences in recurrence free survival. This needs at least being commented on
Yes, we have commented it in our paper. Tumor load between groups is balanced (Table 3). Local treatment modality lies on many factors such as costs, dread of side effect and undesirable process of radiotherapy, not only indication of breast-conserving surgery. Thus, we made the decision on type of surgery based on both patients’ and doctors’ opinions and we consider that modified surgery is not simply to mean higher tumor load.

4 4% difference in patients with more than 3 involved lymph nodes comparing Tam with toremifene / see also differences for stage III / see hugh differences in local control in table 7
We think our answer to question 3 could also answer this question.

5 Please state proportion in each group having received adjuvant chemotherapy
Yes, it was a serious careless omission of us. We have supplemented information of this aspect, including number of people who received chemotherapy and chemotherapy categories.

6 We all know that premenopausal women have less side effects from tamoxifen than postmenopausal women. Authors should refer to literature which differentiates side effects of SERMs by menopausal status for tamoxifen and toremifene
We have searched relevant literature and found that, as to serious complications such as pulmonary embolism, deep vein thrombosis, and stroke. Those studies mostly focused on postmenopausal patients. The endocrine treatment had clear differential gynaecological side-effect based on different menstrual situation. The action of tamoxifen on the human endometrium in postmenopausal women includes hyperplasia, while in others cause endometrial cystic atrophy. Also, postmenopausal patients treated with tamoxifen may develop endometriosis, adenomyosis and leiomyomata. Tamoxifen disrupts the menstrual cycles and increases the incidence of ovarian cysts in premenopausal breast cancer patients while in postmenopausal patients it induces ovarian cystic tumors and endometriomas. We have referred to these in our paper.

7 The authors should compare toremifene outcome data from other trials with these in this study and explain differences (Ahn et al in JCO 2007).
The trial reported in JCO2007 failed to compare any effect on patients between tor and tam, and its emphasis is survival benefit of tam on very young patients. We referred to this trial just in order to demonstrate feasibility of offering tor to premenopausal breast cancer patients.

8 Some patients were on the drug only for a few months/ please provide SD and ranges for follow-up times
Which part of patients did you mean? 43 patients discontinued endocrine therapy less than 1 year for refusal? or patients in 452 patients who discontinued SERMs therapy for menopause or other inevitable reasons? If it is the former, we are afraid that most of those patients refused to do any further consultation and we failed to collect their follow-up times. If it is the latter, we analyzed them the same as others in accordance with intent-to-treat analysis, not did statistics of follow-up times separately.

9 Please provide data on how patients are followed-up in this setting (yearly mammogram? yearly bone scan/CT chest-abdomen?/) and whether these patients all presented with self detected breast cancers versus screen detected tumors (excellent outcome!!!)
Yes, we have supplemented these data in our paper. Patients in our study all presented with self detected breast cancers.

Minor revisions
1 Data on follow-up oestradiol and FSH levels should be reported (proportion in menopause following 5 years of follow-up) as interaction between ovarian suppression from chemo may interfere with results as several times demonstrated by other groups
Yes, we have supplemented these data. There were 90 patients in TAM group and 76 patients in TOR group who became menopause during endocrine therapy $(p=0.716)$, and some of them turned to AIs therapy $(Table 9, p=0.242)$

2 'A lot of them menstruate again a few days later after chemotherapy'- this may be better 'months' rather than days
Yes, we have revised it in our paper.

3 The authors should discuss the poor value of retrospective data analyses concerning drug side effects/what is a uterine cyst?/ how long after
Yes, we have supplemented discussion of the poor value. Uterine cyst is a careless omission of us, and we mean cervical cyst, and we have revised it in our paper. All objective adverse events happened during the period of taking endocrine drugs. We found that gynaecological side-effect such as ovarian cysts and uterine fibroids always occurred a few months later after taking drugs. As to subjective side effects, especially some transient displeasure, such as skin rash, nausea, vomit, and so on, patients always forgot the occurred time, the seriousness, or the possible causes. In that case, we are afraid that these results should be interpreted with caution and this study failed to reveal how long after taking drugs these subjective complications occurred

4 Please report treatment discontinuation/compliance between groups
Yes, we have supplemented these data in Table 9.

5 It is always better to report the first event as number of events in table 7 is larger than overall number of patients with an event
Yes, we have reported it. In TAM group, there were 12 patients who had multiple site recurrence, of which 7 had multiple sites of distant metastases, 5 had concurrent logoregional and one or two sites of distant recurrence. In TOR
goup, there was 1 patient who had concomitant bone and liver metastases.

Dr. Rupert’s questions:
1. How were the cohorts defined? In other words, who decided which patient will receive toremifen or tamoxifen? On what basis was the decision made?
One doctor prescribed patients tamoxifen routinely, and another doctor toremifene, based on their habits and experiences.

2. Authors apparently defined premenopausal simply by age #50. Are there any data concerning hormone levels? This needs to be resolved! In the discussion section, it is stated that E2 and FSH levels were monitored!
E2 and FSH levels of all patients before and after surgery were indeed monitored, and by chance, 452 patients entered last analysis were all no older than 50, so we used this incorrect expression by imprudence. We have revised it in our paper.

3. Was a sample-size calculation performed?
Since our study is a retrospective study, we did not performed sample-size calculation in advance. Nevertheless, after data finish, we calculated that the precise can reach 0.25 at least based on number of patients we obtained (RR=0.74, sample-size =430, α =0.95)

4. Authors state in the methods section that all patients with >3 axillary lymph nodes received radiotherapy independent of breast conservation or mastectomy. Does that mean that not all patients treated with breast conservation were irradiated? Again, this is crucial as there was an imbalance in the local control between the two groups. In other words, all outcome differences may be simply explained by radiotherapy.
All patients with >3 axillary lymph nodes OR treated with breast conservation were irradiated. In former version of our paper, we analyzed radiotherapy as a potentially independent prognosis factor, but considering that radiotherapy is closely correlative to numbers of lymph nodes and breast conservation surgery, we combined it into surgery modalities. That is to say, there are 3 different local control modalities in our study: BCS+RT, Modified, Modified+RT. We think this handling is more reasonable than the former version. It was not an independent prognosis factor for RFS or OS in our study.

5. What chemotherapeutic regimens were used? Was there any difference in the use of taxanes? Was there any difference in duration or intensity of chemotherapy?
Yes, it was a serious careless omission of us. We have supplemented information of this aspect, including number of people who received chemotherapy, chemotherapy categories, duration and intensity.

6. Was the any difference in the proportion of patients who discontinued treatment between the two groups?
No, there wasn’t. It can be seen in supplemented Table 9.

7. Authors use word such as “assigned to” “accrue” or “prospective follow up” which would rather fit a prospective study. On the other hand, the manuscript is called “a retrospective cohort study”
Yes, these words were incorrect. We have revised them in our paper.

8. In introduction section of the abstract, I would rather state that endocrine therapy for premenopausal women consists of tamoxifen and/or ovarian suppression.
Yes, we have revised it in our paper.

We hope revision version of our paper is better than the previous one and we are wholehearted to receive your further advice.
Best wishes.
Sincerely yours,

RanGu, Fengxisu