Author's response to reviews

Title: Adjuvant Trastuzumab in the Treatment of HER-2-Positive Early Breast Cancer: A meta-analyses with 9117 patients.

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Author's response to reviews: see over
Dear reviewer: David Miles

We are grateful regard your attention to our manuscript. We understand the real importance of the suggested corrections and we reviewed this manuscript following all the recommendations. The major compulsory revision was extrictely followed.

General
The authors have conducted a 'meta-analysis' of the adjuvant trastuzumab trails in early stage breast cancer. I personally remain anxious about the term 'meta-analysis' with respect to this sort of publication. These data do not refer to the source data of each individual trial as per the Oxford overviews but rather are a summary of the data, weighted by trial size. Given the homogeneity of results and the admitted 'appropriate' powering of the majority of the studies, the summary data hold no surprises. The results are therefore perhaps, at best, of moderate interest only.

For us systematic reviews provide a rational synthesis of the research base and offer clear advantages to healthcare decision-makers. They attempt to overcome the deficiencies of narrative reviews and polemics by applying the same rigorous standards to secondary research (where the unit of study is other research studies) as should be applied to primary research (original empirical study). Good systematic reviews take great care to find all the relevant studies, assess each study for the quality of its design and execution, and combine the findings from individual studies in an unbiased manner. In this way they aim to present a balanced and impartial summary of the existing research evidence. Frequently, such systematic reviews provide a quantitative estimate of net benefit aggregated over all the included studies. Such an approach is termed a meta-analysis. Consequently, this systematic review and meta-analysis was proposed, by the first time, so as to analyze the results from clinical trials that compared only adjuvant trastuzumab treatment for HER2-positive early breast cancer (EBC) to observation. We agree that data do not refer to the source data of each individual trial as per the Oxford overviews. However, basically two forms exist to become a meta-analysis (individual patients and published studies). We performed a meta-analysis based in data source extracted from abstracted data or published studies. Both have its advantages and limitations. For this, we change the heading of the manuscript (Adjuvant Trastuzumab in the Treatment of HER-2-Positive Early Breast Cancer: A meta-analyses of published randomized trials.) and introduce one section in the discussion (limitations of our study). Due to the variety of the different studies it was not possible to identify sub-groups of patients, whom chemotherapy is not necessary (patients with estrogen receptor-positive and HER-2/neu-positive disease, patients with negative lymph nodes and tumors < 1 cm) and for whom trastuzumab alone might represent appropriate adjuvant therapy. Thus these data can guide new clinical trials and confirm the utility of our study. Moreover, we demonstrate a reduction in the incidence of other tumors no breast cancer in trastuzumab arms, described fact only in the study of NSABP-31.
Question 1
For a meta-analysis of efficacy and toxicity, there is too much discussion (in the wrong place) on the pharmacoecomics. No formal assessments have been done and while the fiscal impact is of greatest importance, this discussion adds little to the paper as a whole.

We agree to this question. In this way we remove the discussion on cost of the text.

Question 2
I remain confused about the subject of 'second no breast cancer ca' the discussion mentions cerebral metastases in this section. Is this what was meant or is there truly a reduction in risk of other cancers (I do not remember this from original publications)

We define better the term “second tumor no breast cancer” and introduce a paragraph in the discussion on this data.

Question 3
No comment is made about the heterogeneity of the cardiac data and the 2nd sentence on p17 with respect to cardiac toxicity makes no sense

Commentaries on the cardiac toxicity had been made. We made a random analysis and create a table of cardiac safety with trastuzumab in early breast cancer (table-2).

We would appreciate if you could publish our analysis

Regards,
Gustavo Viani
Cover letter

Dear reviewer: Andrew Roddam

We are grateful for your attention to our manuscript. We understand the real importance of the suggested corrections, and we reviewed this manuscript following all the recommendations. The major compulsory revision was strictly followed.

Question 1-3
We included the analysis with random effect to evaluate the heterogeneity between the studies and the result was different (p value insignificant). In this way, in the discussion section (cardio toxicity), we discussed the factors that could explain the differences of cardiac toxicity. Moreover, we included a table with the characteristics of the studies and cardiac toxicity.

Minor essential revisions
Question 1 and 2
Table-1 was corrected, we described in such detail each of the trials and the result section (description of studies)
Question 3
The text abbreviations were corrected.
Question 4
The quality scores of studies were introduced in the table-1.
Question 5
The sentence was corrected or excluded.
Question 6
“Only” was removed
Question 7
“Likelihood of brain metastases was 0.33-fold” was corrected.
Question 8
The start of discussion was corrected according to your suggestion.
Question 9
The discussion of costs was removed.

We would appreciate if you could publish our analysis

Regards,

Gustavo Viani