Reviewer's report

Title: Impact of modern chemotherapy on the survival of women presenting with de novo metastatic breast cancer

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Reviewer: Vivianne C Tjan-Heijnen

Reviewer's report:

Major comments

methods
1. In the methods section, paragraph statistical analysis the authors do not state what test they used to determine the p-values stated in table 2.

results
2. Table 2 with patient characteristics is not clear and not complete. The meaning/definition of the 2 numbers behind each variable is unknown (most likely number and percentage, but it is not clearly stated). If it is indeed number and percentages than at least some of the given numbers and percentages are incorrect. For example the presence of bone metastases. In period A, 84 patients have bone metastases, which is not 61% as now stated but 56%. In period B, 82 patients have bone metastases, which is not 61% as stated but 67%. The percentage of 61% in both groups is now stated as being equal which does not correlate with a p-value of 0.008. As stated in comment 1, it is not clear what and with which test the p-value is reported.

In the methods section it is stated that histology was classified as either inflammatory or invasive ductal but in table 2 the used terms are inflammatory versus non-inflammatory. If you add up the numbers of patients in both groups the total amount of patients is more than the total amount of included patients. Furthermore, the range of age should be given in addition to median age in years.

3. In both univariate and multivariate analyses several factors influencing survival of metastatic breast cancer is tested, however no information of the actual median survival times of these patients is provided. Given the patient characteristics in table 2 (high rates of palliative chemotherapy (69% in period A and 89% in period B) and low median age in both periods), the median survival of patients in both periods is essential to determine whether this chosen cohort is representative of general primary metastatic breast cancer patients.

4. In the paragraph on univariate analyses, the authors state that there is no difference in survival among patients receiving chemotherapy category A compared with patients receiving chemotherapy category A+B (p=0.13). However, they also state that there is a difference in survival in patients receiving
HER2-directed agents compared with patients not receiving HER2-directed agents (p=0.15). With the same not-statistically significant different results these statements seem contradictory.

5. In the paragraph on stepwise multivariate analysis, the whole first section is a description of methods and is possibly more appropriate in the method section.

More in general:
• the numbers of patients included is too low (n=274), to make any firm conclusions.
• Many missings in HER2 status and other items (table 2), which compromises any conclusion to be drawn.
• Unclear: is a comparable treatment of ovarian function suppression such as surgery included in the LHRH agonist analyses, and/or was LHRH agonist continued after progression.
• Multivariate analysis: bisphosphonates comes up as a significant factor. However, was the ER status included and corrected for?, as it is likely that especially in the ER positive group bisphosphonates were given because of bone metastases, where the ER positive patient group with bone metastases has the best survival as we know from other studies.

discussion

6. In table 6 all previously published studies on the research question of interest are summarized. However, again this table is not clear. They did not clarify the used abbreviations.

Furthermore, not all information seems correct. The study by Ruiterkamp et al. did only include women with primary distant metastatic breast cancer (Citation: According to the database of the Netherlands Cancer Registry, 160,595 new patients were diagnosed with invasive breast cancer in the period 1995–2008. Of these patients, 8,031 (5.0%) had distant metastases at diagnosis (stage IV disease). from Ruiterkamp J, Ernst MF, de Munck L, et al. Improved survival of patients with primary distant metastatic breast cancer in the period of 1995-2008. A nationwide population-based study in the Netherlands. Breast Cancer Res Treat 2011;128:495-503.) and not patients with recurrent metastatic breast cancer as stated in table 6.

7. The authors state in the discussion section, in paragraph 3 that both this study as well as the study by Andre et al. reported overall improvement in survival. As stated in comment 3, there are no survival times reported in this study and therefore this statement is not supported by any data.

Minor comments

8. The authors use the term de novo metastatic breast cancer, which could be changed into the more commonly used term of primary distant metastatic breast cancer.
9. In the introduction section, the authors state their research question which is well defined and clearly stated. Furthermore, they refer to other studies previously performed with the same research question (Giordano et al, reference number 4 and Chia et al, references number 5). However, this is far from a complete overview of previously published studies on this subject, as the authors also show in table 6 and state in the discussion. I suggest to refer to all six studies described in table 6 in the introduction, in the paragraph on the previous studies with similar research questions.

10. In the introduction, in the second paragraph ration is misspelled (should be ratio).

11. In the introduction section, third paragraph the term metastatic breast cancer is mentioned for the first time. After that, the authors use the abbreviation MBC. In order to do so, the used abbreviation should be stated after the first use of the complete term (e.g. metastatic breast cancer (MBC)).

discussion

12. In the discussion section, third paragraph the sentence ‘We found no advantage to the use of the newer chemotherapeutic agents and Anders found no survival advantage for women with hormone receptor-negative disease. It is not clear what the authors mean with Anders. Maybe they misspelled Andre and are they referring to the study by Andre et al. but no reference number is given.

13. The final sentence is incorrect; the impact ...... appears to be is minimal.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'. 