Reviewer's report

Title: Incidence of chemotherapy-induced amenorrhea associated with epirubicin, docetaxel, and navelbine in younger breast cancer patients

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Reviewer: Mikkel Rosendahl

Reviewer's report:

In the manuscript “Incidence of chemotherapy-induced amenorrhea associated with epirubicin, docetaxel and navelbine in younger breast cancer patients” the authors analyse retrospectively in 170 patients the self-reported incidence of cessation of menses for at least three months. The authors use this as a marker of amenorrhea. They find that the risk of amenorrhoea is associated with increased age, administration of cyclophosphamid and tamoxifen.

Overall the paper is very well written in clear and concise English and has the appropriate lengt.

Nevertheless the study seems to have been written without basic insight in ovarian physiology. There are some concerns with the setup and the conclusions:

Major Compulsory Revisions and general remarks:

Amenorrhea and prognosis:

It is nor clear whether amenorrhea itself has an impact on prognosis or whether it is a marker of higher bio-availability causing both ovarian destruction and tumour-cell destruction. See Rosendahl et al. Eur J Cancer, 2009 for references.

The definition of amenorrhoea:

The authors evaluate “amenorrhoea” 6 and 12 months after initiation of chemotherapy. Six months since the initiation of chemotherapy is much too soon! Any patient receiving chemotherapy will experience irregular menses – no matter the age. This is merely evidence of chemotherapy-induced destruction of the granulosa cells in the growing follicles resulting in oligo- or amenorrhea. It is NOT evidence of destruction of the ovarian reserve. The author should acknowledge this.

Administration of tamoixifen:

Tamoxifen has various effects in different tissues. In the endometrium is an agonist, in the breast tissue an antagonist. In the ovaries, tamoxifen results in follicular stimulation and – like clomiphene citrate – can be used to stimulate the ovaries for IVF (See Oktay, Fertil Steril).
So – YES – tamoxifene will cause both increase in FSH and oligo- amenorrhea but also an increase in estradiol! These changes are physiological and simply evidence of multiple follicles resulting in anovulation. Tamoxifen is NOT responsible for destruction of primordial follicles and the interpretation – that tamoxifen causes premature ovarian failure is incorrect. Anti Müllerian Hormone can be used to evaluate the pool of resting primordial follicles in the ovaries. In a follow-up study (Rosendahl et al, Hum Reprod 2008) the authors found no difference in AMH between users and non-users of tamoxifen suggesting that only growing follicles were influenced by this. It may be responsible for the amenorrhoea but this is physiological and unrelated to the ovarian prognosis. It would be like suggesting that amenorrhoea during breastfeeding causes premature ovarian failure.

The authors are suggested to include these reflections in the manuscript.

Minor essential revisions and specific comments:

1. Methods – patients: Had some patients received chemotherapy previously? This is unclear.
2. Treatment: What were the dose-intensity percentiles of treatment groups? Did all groups receive 100% dose? Reduced dose may affect outcome. How was this regulated
3. treatment, third-last line: “….inhibitor at least 2-year tamoxifen….” Don’t understand it.
4. Treatment: Follow up time, shortest was 1 year. From initiation of chemo? What was the longest and what was mean or median follow-up?
5. Statistics: Why was age <40 / > 40 used. Why a dichotomous variable not a continuous?
6. Page 6, results – about age: last line: “ overall, these results….” Move to discussion.
7. results, last lines of univariate analysis: “…for too little time…” Don’t understand.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

'I declare that I have no competing interests' below.