Fenretinide in the prevention of breast cancer in premenopausal women: fluke or fact?

This issue of Annals of Oncology includes a very interesting manuscript reporting the 15-year follow-up of two-thirds of the women initially randomized in a phase III trial of 5 years of fenretinide versus observation [1]. These women, who were aged 30–70 years old at the time of randomization had completed either breast conserving surgery or mastectomy for primary breast cancer with curative intent but were given no systemic therapy after primary surgical and/or radiation treatment. Women were randomized to the study either immediately (about half of all eligible subjects) or within 10 years of primary treatment. The study was initiated in March 1987 with 2867 assessable patients and the main results after 8 years were reported in 1999 [2]. At that time, the study overall showed no difference in contralateral and/or ipsilateral breast cancer rates, but a post-hoc analysis suggested a significant treatment interaction with menopausal status, with a 35% reduction in new breast cancers in premenopausal women (or women aged less than 50 years) and an opposite trend in post-menopausal women (or women aged more than 50 years).

Subsequently only those 1739 patients being seen in the main study centre, Instituto Nazionale per lo Studio e la Cura dei Tumori, Milan were regularly followed-up as per protocol, with biannual visits including clinical exam, blood tests, mammography and chest x-rays every year and a bone scan every 18 months. Follow-up on the remaining 40% of participants was variable and is not reported in the current paper.

In addition to this reporting of data on less than two-thirds of the original study population, the authors are missing other information that is crucial to interpreting these data. They have not told us whether patients’ primary tumors were estrogen receptor (ER) positive (+ve) or negative (–ve) nor whether the contralateral or ipsilateral recurrences were ER+ve and ER–ve. Clearly this information, and a breakdown of the results by it, are crucial to the interpretation of these data. The authors do state that in another paper [3] it has been shown, that the effect of fenretinide in prevention is seen in premenopausal women regardless of the hormone receptor expression of the primary cancer [4]. Their own data, however, apparently do not include receptor status [2].

The authors state in their discussion that the subset analysis of the data from this trial, by premenopausal and post-menopausal subgroups, was not a pre-planned analysis. They therefore correctly comment that their observation is hypothesis generating and requires a further randomized study to confirm these results. The lack of pre-planned analysis by age or menopausal status, the fact that data is available on fewer than two-thirds of women in the study, as well as the lack of information on hormone receptor status of primaries or of contralateral or ipsilateral new breast cancers leave more questions unanswered than answered in this study.

Nonetheless, there is considerable preclinical data to suggest that fenretinide has the capacity to act as a preventive agent against in both ER+ve and PR–ve breast cancer cells [5]. Fenretinide has also been shown to prevent recurrence in ovarian cancer [6] and in cell models of BRCA1 mutated cells [7]. These observations would fit well with the data described in this manuscript.

It is certainly also true that approaches to prevention are particularly lacking in both premenopausal or younger women and in women with ER–ve breast cancer. Tamoxifen alone has been shown to be effective in premenopausal women [8, 9] but neitherRaloxifene [10, 11] nor any of the aromatase inhibitors (AIs) [12, J. Cuzick, pers. comm., 2006] have been studied for prevention in younger or premenopausal women because of lack of demonstrated safety. It is in fact believed that in premenopausal women an AI may cause surges of estrogen, which may actually be detrimental in the setting of previous breast cancer. Thus, this tantalizing observation suggesting that fenretinide may reduce the risk of contralateral and ipsilateral breast cancers following primary breast cancer surgery in premenopausal women is of great interest. Further information regarding details of receptor status and particularly follow-up status of the other 40% of women in this study will hopefully be forthcoming.

In the meantime, further investigation of the role of fentretinide as a prevention for ipsilateral and/or contralateral recurrence and perhaps as well for prevention of distant disease in women with previous breast cancer should be considered.

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