Re: Ovarian Ablation or Suppression in Premenopausal Early Breast Cancer: Results from the International Adjuvant Breast Cancer Ovarian Ablation or Suppression Randomized Trial

According to the Adjuvant Breast Cancer Trials Collaborative Group (ABCTCG) (1), women were defined as pre- or perimenopausal if their last menstrual period had occurred within the 12 months before breast diagnostic surgery. Dates for the last menstrual period may be inaccurate due to poor
patient recollection, miscommunication, or abnormal bleeding. Previous studies reported that women were considered premenopausal if they had their normal last menstrual period in the last 6–12 months before surgery (2). However, most studies have been retrospective reviews of clinical records, in which a major uncertainty has been the date of the last menstruation. In a retrospective unplanned analysis to determine whether the timing of surgery during the menstrual cycle influences outcome (3), the information about the last menstrual period was considered reliable in only 79% of the patients enrolled in the original clinical trial (4). Moreover, some women may have ovarian function activity and estradiol secretion without evidence of menses.

The authors (1) report that no assessment or selection based on postchemotherapy menopausal status was required because “a proportion of patients resume substantial ovarian estrogen production over the course of the first year postchemotherapy.” They promptly recognize that this fact may have precluded the identification of an ovarian ablation or suppression (OAS)–associated benefit. Conversely, continuation of regular menses after treatment does not necessarily imply that the ovaries have escaped damage, and patients who continue to ovulate after chemotherapy remain at risk of undergoing premature menopause after treatment. In addition, based only on reported menstrual cycle history, at least 16% of premenopausal women are misclassified following chemotherapy.

Alteration of pituitary and/or ovarian hormone levels driven by the effects of cytotoxic drugs on ovarian function can be sharp and immediate. Estrogen, progesterone, and luteinizing hormone levels of breast cancer patients are affected within the first courses of chemotherapy. The most benefit has been reported in patients with chemotherapy-induced amenorrhea who receive “suboptimal” chemotherapy (5). Younger women who did not receive chemotherapy were considered to have the greatest benefit from OAS. In fact, according to the ABCTCG trial, in younger women (aged <40 years), who did not receive chemotherapy, there was a suggestion of a potentially useful clinical benefit, which was slightly greater if women with estrogen receptor (ER)–negative breast cancer were excluded (1). According to the Zoladex in Premenopausal Patients Trial (6), the effect of goserelin (Zoladex), a luteinizing hormone–releasing hormone analog, was greatest in patients with ER-positive tumors who had not received chemotherapy. A subgroup analysis of the International Breast Cancer Study Group Trial VIII (7) found that younger women (≤39 years), a patient population least likely to develop chemotherapy-induced amenorrhea, had a statistically significant benefit of combined treatment (cyclophosphamide–methotrexate–fluorouracil followed by goserelin) versus cyclophosphamide–methotrexate–fluorouracil alone.

Based on these findings, if one period within the previous 12 months qualified the patient as premenopausal for purposes of the ABCCTCG trial (1), the primary endpoint of this study (rate of overall survival among women who underwent OAS and those who did not) would require exquisite accuracy (endocrine profile) and may be asking more than this premenopausal status definition can give.

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References


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